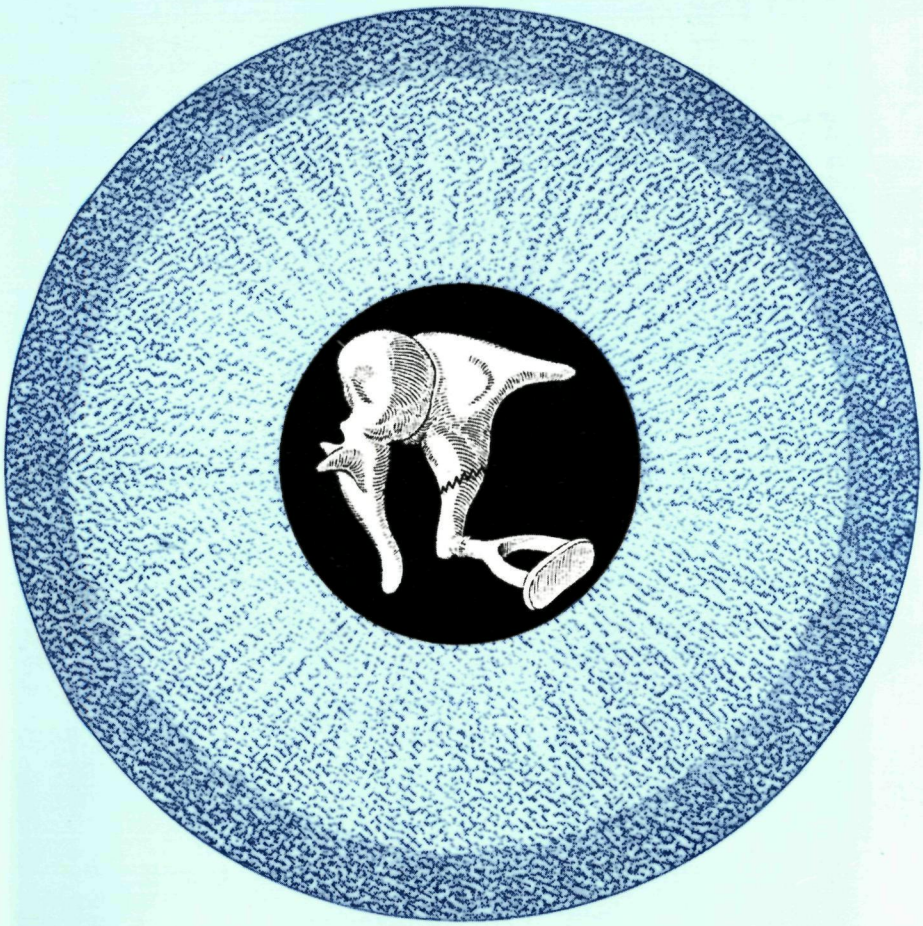
OSTEOGENESIS IMPERFECTA TYPE I

otological and clinical genetic aspects



A.J.T.M. Garretsen

OSTEOGENESIS IMPERFECTA TYPE I

OTOLOGICAL AND CLINICAL GENETIC ASPECTS

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OSTEOGENESIS IMPERFECTA TYPE I

OTOLOGICAL AND CLINICAL GENETIC ASPECTS

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THESIS

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by

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born in Arnhem

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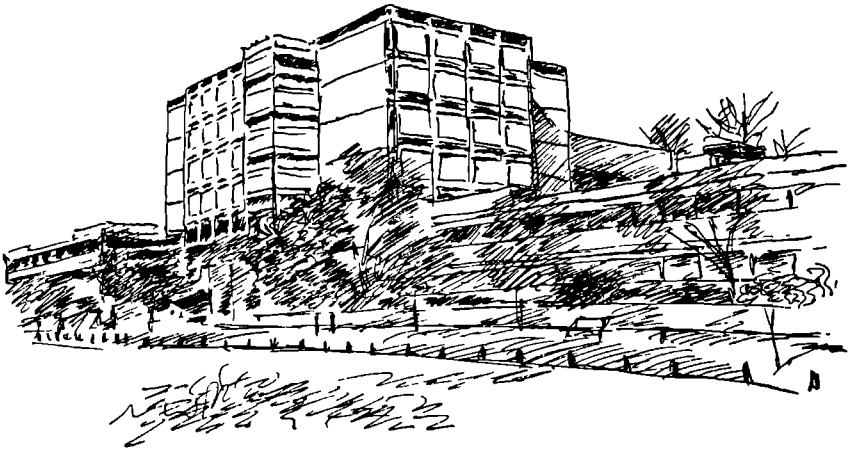

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE STUDY

Introduction

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited conditions arising from a variety of biochemical and morphological collagen defects. Apart from the brittleness of the bones and the susceptibility of affected individuals to bone fractures from very mild trauma, other manifestations of abnormalities in bones, teeth, sclerae, ligaments and other collagen containing tissues indicate the heterogeneity of the condition. Although the "brittle bone" aspect of OI is its hallmark feature, OI is a generalized disorder of connective tissue. Affected individuals may have non-osseous features such as blue sclerae, hearing loss, dentinogenesis imperfecta[1], growth deficiency, loose or dislocated joints, cardiopulmonary abnormalities,[2,3] easy bruising, hypermetabolic states with excessive sweating and metabolic acidosis,[4,5] basilar impression and other neurological complications.[6,7]

The incidence of OI is estimated to be 1 in 20,000-30,000 newborns;[8-13] whereas Byers stated that OI phenotypes occur in about 1 in 5000 to 1 in 10,000 subjects.[14] The prevalence corresponds with the smaller incidence.[15] It is estimated that there are approximately 600 OI sufferers in the Netherlands, most of whom have OI type I.

Until recently, patients were classified as having a congenital form or a tardive form of OI. In the "congenita" and "tarda" classification, congenita cases were generally severe, because, by definition, the diagnosis could be made at birth. This group included cases with the lethal form as well as the cases more likely to survive. There was no accounting for genetic patterns. Tarda cases were those recognized beyond the neonatal period. These cases were generally milder than congenita cases and could anticipate further improvement subsequent to puberty. Emphasis on the time of diagnosis failed to account for cases noted at birth in families with a relatively mild form of the disease and the considerable variation in the prognosis of congenita cases.

The classification now in general use among geneticists was first proposed by Sillence et al.[8] in 1979 and has been extended since then by him and others.[1,16-19] The clinical, radiographic and genetic classification divides OI into four types (Table 1). Although some cases and/or families do not fit into any of the Sillence OI types as precisely defined,[20] the broad groups have provided a common groundwork for discussion and

Table 1: Classification of Osteogenesis Imperfecta Syndromes[1 8 11 14 19 34 36 41]

OI type*	Description of clinical features	Biochemical and genetic abnormalities
I AD	Normal, sometimes mild short stature Mild-to moderate bone fragility with little or no deformity Blue sclerae Hearing loss in almost 50% Dentinogenesis imperfecta (DI) is rare OI type IA DI is absent OI type IB DI is present Easy bruising	Common 'Non-functional' COL1A1 allele Rare Substitution for glycine residue in carboxyl terminal telopeptide of α 1(I) Substitution of glycine at position 94 of the the triple helix in pro α 1(I) Exon deletion in pro-α-2(I) triple helical domain
II AD	Lethal in the perinatal period Extreme fragility connective tissue, multiple fractures in utero, usually interuterine growth retardation Minimal calvarial mineralisation, soft large cranium Micromelia, long bones crumped and bowed, ribs beaded, platyspondyly	Common Substitutions for glycyl residues in the triple helical domain of the α 1(I) and α-2(I) chain Rare Rearrangements in COL1A1/COL1A2 Exon deletions in the triple helical domain Substitutions and small deletions in the non-triple helical carboxyl-terminal propeptide Tripeptide deletion in pro-α-1(I) triple helix
AR		Small deletion in α-2(I) on the background of null allele
III AD	Progressively deforming bones, usually with moderate deformity at birth, caused by severe fragility of bones and fractures in utero Stature very short, kyphoscoliosis, severe osteoporosis Sclerae variable in colour, often lighten with age Dentinogenesis imperfecta common Hearing loss common	Point mutations in COL1A1 and COL1A2 gene
AR		Frameshift in COL1A2 that prevents the incorporation of pro-α-2(I) chains
IV AD	Normal sclerae (slightly blue or greyish in infancy) Mild to moderate bone deformity, often bowing of long bones, scoliosis and variable short stature Skeletal fragility and osteoporosis more severe than type I Dentinogenesis imperfecta (DI) OI type IVB (mostly) DI is present OI type IVA DI is absent Hearing loss occurs in some	Point mutations in COL1A1 and COL1A2 gene

* AD, autosomal dominant, AR, autosomal recessive

research. In 1987 during the Third International Conference on Osteogenesis Imperfecta in Pavia, Italy, consensus was achieved to retain the Sillence classification while research continued, to add a more molecular emphasis to the nomenclature.[21]

History

Historical investigation is complicated by the fact that OI has been discussed under numerous eponyms (Table 2).[22]

The discovery in 1967 of OI in an Egyptian infant dating from the 21st Dynasty (about 1000 B.C.) represents the earliest known case of the disease (Figure 1).[23]

According to Seedorff, the first case suggestive of OI was that of a mythical Danish prince, Ivar Benløs (boneless), son of Aslaug and King Ragnar Lodbrog, who lived in the ninth century and who had to be carried into battle on a shield as he was unable to walk on his soft legs.[24] Unlike the Egyptian Mummy, further studies on his bones were allegedly prevented by William the Conqueror who, after his conquest, opened Ivar's grave and burnt the body.

Table 2: Numerous eponyms under which osteogenesis imperfecta has been discussed[22]

Adair-Dighton disease (syndrome)	Lobstein's disease
Aplasia periostalis	Malacia myeloplastica
Blegvad Haxthausen syndrome[102]	Maladie de Porak-Durante
Blue sclera syndrome	Maladie de Lobstein
Blue sclerotics and brittle bones	Micromelia annularis chondromalacia
Blue scleras and fragilitas ossium	Molities ossium
Brittle bones and blue sclerae	Osseous fragility
Dark sclerotics and fragilitas ossium	Osteogenesis imperfecta congenita (Vrolik)
Dysplasie périostale	Osteogenesis imperfecta tarda
Dystrophie périostale	Osteomalacia congenita
Eddowes disease (syndrome)	Osteomyopathia
Ekman syndrome	Osteoporosis foetalis
Ekman-Lobstein syndrome	Osteopsathyrosis idiopathica (Lobstein)
Fetal rickets	Osteopsathyrosis foetalis
Fragile bones	Osteitis parenchymatosa chronica
Fragilitas vitrea ossium	Rachitis congenita
Fragilité osseuse congénitale	Spurway - Eddowes syndrome
Hereditary fibrous osteodysplasia	Van der Hoeve - De Kleyn syndrome
Hereditary hypoplasia of the mesenchyme	Vrolik disease (syndrome)

Figure 1: Infant in cartonnage case from the 21st Dynasty (c. 1000 B.C.) in the form of an Osiris figure. The height is 73 cm and it is remarkable that the case is surmounted by double plumes. It resembles closely a normal figure of Ptah-Seker-Osiris.
The case was found by Professor John Garstang in 1905 at a site known as the Speos Artemidos in the necropolis of Beni Hasan, the site of an ancient Egyptian town on the East Bank of the Nile.
The perculiar bowed appearance of the removed and unwrapped bones and the triangular shaped skull suggested to the excavators that the remains were those of a mummified monkey.

Malebranche wrote the first known case report in 1674.[25] He described a 20-year-old mentally retarded male whose bones resembled those of a condemned criminal broken on the wheel. During the next century, other authors described patients suffering from congenital fractures attributed to the fact that their mothers had witnessed the execution of a criminal upon the wheel while the child was in utero.[24]

The first scientific description of the disease was given by Olaus Jakob Ekman, chief surgeon in the Swedish army, who held his medical degree thesis on May 10, 1788 by describing a family afflicted by "congenital osteomalacia" in three generations.[26] This work was resurrected and published by Seedorff in 1949.[24]

That OI affects other organs as well as bones was first noted in 1831 by Edmund Axmann, who suffered from the disease himself as well as two of his brothers and who gave the first clear account of four major characteristics of osteogenesis imperfecta: bone fragility, hypermobile joints permitting easy dislocation, blue sclerae and frail body build.[27] His contribution to medical knowledge was overlooked until 1958 when Caniggia et al. credited him with being the first to recognize some of the complex aspects of what had first been thought to be merely "brittle bone disease".[28]

He also advanced the hypothesis that these defects could be caused by a weakness in fibrous tissues. Lobstein received medical acclaim as the first to recognize the hereditary nature of fragile bones when he described "osteopsathyrosis idiopathica" in 1833, because the work of Ekman (1788)[26] had remained unnoticed for a long time.[29]

The entity Lobstein described probably corresponds with what is now referred to as one of the dominant OI types, according to the Sillence classification.[8] Weil (1981) is not certain whether Lobstein described osteoporosis or osteopsathyrosis.[22] Uptill now, this condition of OI was often seen in the French literature as "la maladie de Lobstein".

In 1849, Vrolik introduced the term "osteogenesis imperfecta" by describing an infant with imperfect osteogenesis, multiple congenital fractures, a large head with probably Wormian bones and who succumbed on the third day of life.[30] This is the first treatise on what in earlier days we would have called OI congenita and nowadays would classify as a mild form of OI type II or a severe form of OI type III, according to Sillence.[8]

For several decades, osteogenesis imperfecta congenita (Vrolik) and osteopsathyrosis

idiopathica (Lobstein) were thought to be two different diseases both related to rickets. Schmidt (1859) concluded from an autopsy that the condition would be best described as chronic parenchymatous osteitis, differing from osteomalacia, rachitis or ordinary osteitis.[31] This may be the first histological description of OI. Stilling (1889) disproved the relationship between rickets and OI on histological grounds.[32] In 1898, Kaufmann recognized that OI, achondroplasia and rickets were different entities.[33] Histological examinations by Looser (1906) provided conclusive evidence that the microscopic picture of OI and osteopsathyrosis was similar.[34] Looser also made a distinction between OI congenita and OI tarda.

Unaware of Axmann's earlier report (1831), Spurway (1896) and Eddowes (1900) once again observed that blue sclerae was a finding associated with the hereditary tendency to fracture.[35,36]

Preiswerk (1912) observed that the incisors of a four-year-old girl afflicted with osteogenesis imperfecta were fairly small and had a brownish-grey color shining through them.[37] He emphasized that this was what he called tooth rickets or tooth involvement with osteogenesis imperfecta independent of osteogenesis imperfecta of the bone of the mandible. Bamberg and Huldschinsky (1913), searching for a biochemical explanation, failed to find abnormalities in serum calcium and phosphorus.[38] Ostheimer (1914) described a young affected child with a warm, moist skin.[39] In 1918 Voorhoeve emphasized the possibility that osteogenesis imperfecta was due to a genetic disorder of the mesenchyme.[40] He stated that the presence of labyrinthine involvement strengthened his theory of mesenchymal inferiority. Bauer (1920) may have been the first to describe symptoms of a haemorrhagic tendency when he noted that OI patients were highly susceptible to bruising.[41] He attributed the abnormalities to "mesenchymal inferiority" and thorough investigations of dental tissues, cartilage, skin and blood vessels, summarized in 1940, made him the foremost proponent of a generalized mesenchymal disorder as the cause of OI.[42]

The first author who added hearing impairment to fractures and blue sclerae was Adair-Dighton (1912), ignorant of the fact that this was the first description of the triad of OI.[43] His reference to "nerve deafness which started three months after birth of child" in a woman seen 18 months later seems quite casual. It is probably more accurate to credit Dent with this finding, because in 1897 he described a case of

fragilitas ossium and deafness in the absence of blue sclerae.[44] However, by studying the picture of the patient and the skiagraphs of his deformed and bowed bones, it could have been a case of OI type IV, which is known to be associated with sclerae of grayish blue or even white.

Van der Hoeve and De Kleyn, who eponymed the syndrome, presented a paper to a clinical meeting in Utrecht in 1916 in which they claimed that the deafness in this triad was conductive in type and clinically indistinguishable from otosclerosis. The hearing loss in one family occurred in each of the four generations except the youngest one and in 11 out of 22 family members. However, their paper was not published until 1917 in Dutch and until 1918 in German.[45,46] The X-ray studies of their patients were done by Stenvers who described a calcareous deposit of sclerosis of the petrous bone.[47] This is the first reported use of X-rays of the petrous pyramid to diagnose involvement by osteogenesis imperfecta. He was also the first to notice an abnormal blueness of the drums. By that time, Bronson (1917) had independently described 19 cases with hearing loss associated with bony fragility in one family and wrote the most comprehensive review of the subject to that date.[48] It would appear that she was the first to describe the symptom of dizziness in OI patients whose hearing was impaired. Bronson adduced the theory that the deposition of calcium salts in the middle ear might be responsible for the hearing loss. The otological examination of her patients was performed by Fraser (1919) who found "flamingo pink" colour over the promontory in some patients, corresponding with what is nowadays known as Schwartze's sign.[49] In addition, he found hearing loss of the conductive type and in one patient vertigo. It was Fraser's clinical opinion that the deafness in OI was due to otosclerosis. Ruttin (1922) reported otosclerotic placques at the anterior border of the oval window of patients who had blue sclerae and a history of multiple fractures.[50] Weber (1930) noted some similarity between the callus of a healing fracture in osteogenesis imperfecta weblike pathologic fiber bone and that of the so-called blue bone in otosclerosis.[51] He assumed that in addition to the similar mode of the hereditary transmission of the two diseases and the frequent association of otosclerosis with osteogenesis imperfecta and blue sclerae, the histogenic relationship between the two diseases pointed to a common genesis.[52] Weber's ideas have started a chain reaction of misunderstandings for several decades. Until the

1970s, the changes in the middle ear in osteogenesis imperfecta were considered to be a severe form of otosclerosis because otosclerotic changes were found in histologic examinations of temporal bones.[53 55] In otosclerosis four stages in the development of the otosclerotic lesion are usually seen: the first stage is the formation of an active otospongiotic lesion with large resorption spaces containing cellular fibrous tissue; subsequently an immature basophilic bone is formed; in the third phase remodelling with resorption and new bone formation takes place, resulting in a more mature acidophilic bone with a laminated matrix; finally, an inactive highly mineralized otosclerotic bone with a mosaic-like appearance is formed.[56,57] Indeed in some rare cases of osteogenesis imperfecta the histopathologic changes in the footplate resembles the early otospongiotic lesion of otosclerosis like Weber (1930) believed was right.[51]

For many years this problem remained unsolved whether the changes in OI should belong to the disease itself or could be determined as a severe form of otosclerosis.[53 55,58-63] The presence of early otospongitic lesions advcates the otosclerosis theory, however the fact that it only occurs in rare congenital forms of OI pleads strongly against it. In favour of the OI theory was revealed that a greater degree of structural disorganization and larger resorption spaces of the stapedial lesion in OI distinguished the two conditions.[64-66] There is also a difference between the appearance of the stapes suprastructures in OI and otosclerosis, e.g. ossicular discontinuity and even fractures of the crura. Only in a few cases proper histologic examination of the crura demonstrate that some areas were replaced by fibrous connective tissue, most likely due to previous fractures.[61,67-70]

The last decade has shown that there is a clear distinction between some histological features in OI and those in otosclerosis.[70 72] Firstly, there is deficient ossification of the three layers of the otic capsule, the bony walls, and ossicles of the middle ear in OI. Secondly, there is evidence of abnormal ossification. Thirdly, in OI microfractures of the otic capsule and the middle ear ossicles occur.

Biochemical and genetic aspects

Biochemical studies on bone and skin collagen from OI patients have shown that the basic defect involves structures of collagen itself.[73] In recent years, important

discoveries have helped to elucidate the identity of new collagen types, the structure of procollagens and the processes involved in collagen synthesis and degradation.[74-78] In several different types of collagen molecule, quantitative and qualitative changes in type I collagen synthesis causes OI. For type I collagen molecule synthesis, which forms a substantial part of bone matrix, skin, blood vessels and other fibrous tissues, it is necessary to have two α-1(I) and one α-2(I) chains for producing a molecule heterotrimere. Molecule synthesis can be disturbed by several gene mutations that cause a specific OI phenotype. Two genes, COL1A1 located on chromosome 17 and COL2A1 located on chromosome 7, encode the pro-α-1(I) and pro-α-2(I) chains of type I procollagen, respectively.[79,80] These genes each contain more than 50 exons that contain the coding sequence for proteins of about 1400 amino acids.

The genes are coordinately transcribed, the mRNAs are processed and transported to the cytoplasm where they are translated on membrane bound polysomes (Figure 2).

The precursor proteins are inserted through the membrane of the rough endoplasmic reticulum and the signal sequences are cleaved. Each procollagen molecule contains two pro-α-1(I) chains and a single pro-α-2(I) chain. The correct assembly of molecules is directed by interaction of the pro-α-chains through their carboxyl-terminal globular domains. After aggregation in the 2:1 ratio, the chains fold the triple helix from the carboxyl-terminal end towards the amino-terminus. The completed molecule is transported out of the cell through the Golgi apparatus and deposited in the pericellular environment where the two propeptides are cleaved from the molecule and the collagen molecules spontaneously aggregate to form fibril structures. The formation of fibrils depends on the uniformity of subunits and abnormal molecules have highly deleterious effects on fibril structure.

The identification and characterization of mutations in collagen genes has provided unexpected insight into structural requirements for specific domains, the role of these domains in molecular assembly and secretion and, to a lesser extent, the way in which mutation is translated to disease phenotype.

The phenotypic manifestations of mutations in collagen genes reflect the tissue distribution of the gene products.[81] Most mutations in the genes for type I procollagen result in all forms of OI and rare forms of the Ehlers-Danlos syndrome (type VII)

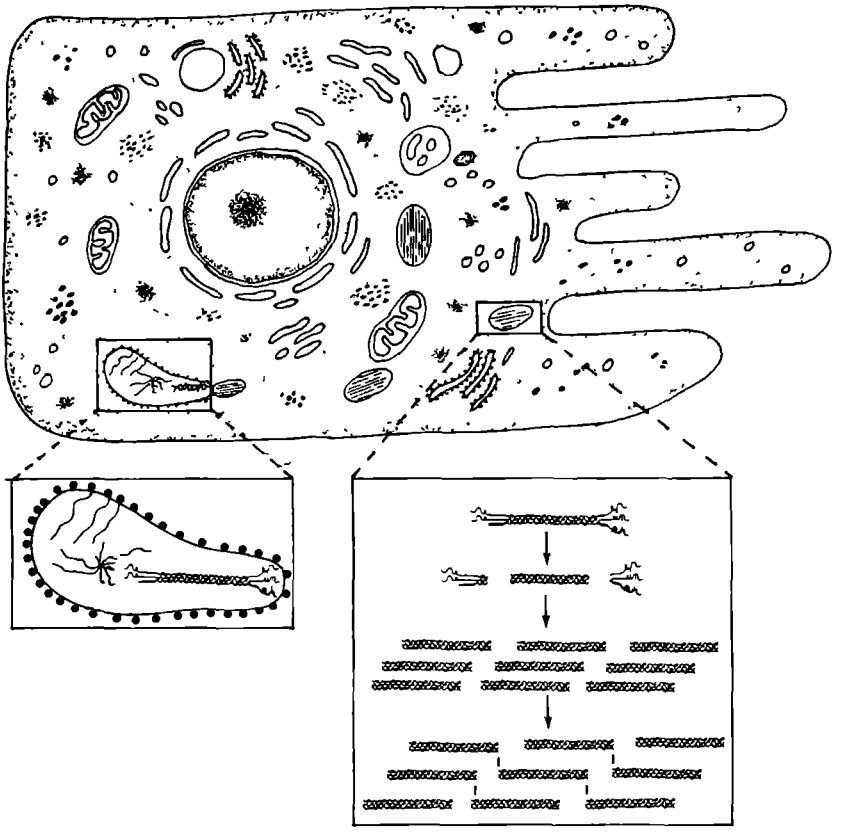

Figure 2: Diagrammatic representation of the assembly of collagen fibers by a fibroblast. Type I collagen, the most common type of collagen, is first synthesized as a precursor molecule that is called type I procollagen and that consists of two identical pro-α-1(I) chains and one slightly different pro-α-2(I) chain. The intracellular assembly of the procollagen molecule occurs primarily in the cisternae of the rough endoplasmatic reticulum (lower left). After procollagen is secreted from fibroblasts, the amino-propeptides on each of the three pro-α chains are cleaved by one proteinase, and the carboxy-propeptides on the three chains are cleaved by a second proteinase (lower right). After the propeptides are cleaved, the collagen molecule spontaneously self-assembles into the quarter-staggered array that gives collagen fibers their characteristic surface pattern of cross-striations.

characterized by hyperextensible joints. Mutations in the genes that encode the chains of type II procollagen result in some of the chondrodysplasias.[82] Mutations in the COL3A1 gene affecting the type III procollagen structure result in a form of the Ehlers-Danlos syndrome (type IV) characterized by vascular and bowel fragility.[83] Furthermore, a mutation in one of the genes of the type IV procollagen (COL4A5) may cause the X-linked Alport syndrome.[84]

The products of the other collagen genes are less accessible because of the restricted range of tissue expression, the relatively low abundance of proteins and the difficulty of growing differentiated cells from tissues such as cartilage (types II, IX, X, XI). As a result of some of these difficulties, the phenotypic consequences of mutations in most collagen genes are still unknown.

During the 1990 International Conference on Osteogenesis Imperfecta in Pavia, Italy, it became clear that more than 80 different mutations of the COL1A1 and COL1A2 genes had been identified in patients with OI to date.[85]

Point mutations are the most common events that lead to OI phenotypes. These mutations 1) may result in substitutions for glycine residues within the triple helix, 2) may produce exon skipping events if they occur in the consensus splice donor or acceptor sites, or 3) may alter the ability of chains to aggregate into molecules if they occur within the domains that encode the carboxyl-terminal propeptide.

In **OI type I**, it has been shown that only half of the normal quantity of pro-α-1(I) collagen is produced, which is mainly caused by mutations in one allele of the COL1A1 gen.[86]

For **OI type II**, the most fully researched form of OI, it is known that various mutations can occur in the COL1A1 gen and in the COL1A2 gen. These mostly comprise point mutations in the COL1A1 gen, which can lead to the substitution of glycine for cystine in the triple-helix part of the α-1(I) chain. In addition, rearrangements can occur in the COL1A1 gen and the COL1A2 gen and a small deletion in het COL1A2 gen. In most cases, these are dominant mutations.[87]

Less research has been conducted into **OI type III**. It has been found that a recessive form exists, in which a frame-shift mutation occurs in the COL1A2 gen, which prevents the incorporation of pro-α-2(I) collagen into the type I collagen molecule so

that they only contain pro-α-1(I) chains.[88,89] A dominant form of OI type III is also possible, involving point mutations in the COL1A1 gen or the COL1A2 gen, which can affect the stability of the triple-helix.[90] One of the resulting phenotypes, in which, for example, cystine is incorporated instead of glycine at a specific site, can be biochemically related to the dominant OI type II (point mutation in the COL1A1 gen) or the dominant OI type IV (point mutation in the COL1A2 gen).

For **OI type IV**, it is reported that in the majority of patients, point mutations in the COL1A2 gen produce changes in about half of the pro-α-2(I) collagen chains.[91] Furthermore, in a minority of cases, small deletions occur in the COL1A2 gen or point mutations in the COL1A1 gen.[92]

The types of mutation in the type I collagen genes which produce the different phenotypes of OI have now become clear. Although these findings are of great interest, such a broad spectrum of abnormalities points to the heterogeneity of the syndrome and to the vast amount of investigation still needed to elucidate the basic biochemical alterations that are expressed. Significant questions remain, however, about how a given collagen sequence alteration contributes to the molecular pathogenesis of OI. The common effects of the different classes of mutations provide a first approach to unifying mechanisms. All the mutations in collagen genes that produce OI, result in the decreased synthesis and secretion of normal type I procollagen.[92] When no abnormal type I procollagen is synthesized, the phenotype is generally quite mild (OI type I). When abnormal molecules are synthesized, the phenotype can range from very mild to lethal, depending on the nature of the mutation and its effect on molecular assembly and stability, on the secretion of abnormal molecules and, presumably, on the ability of the abnormal molecules to disturb normal fibrillogenesis. Abnormal molecules are generally secreted less efficiently than normal ones but, once secreted, can become incorporated into a matrix where they probably disrupt the fibrils in many tissues. In bone, the fibrils that incorporate abnormal molecules may not be mineralized as efficiently as those containing only normal molecules. The number of abnormal molecules that it takes to produce abnormal fibrils may be surprisingly small because of the constraints on molecular dimensions needed to pack molecules into fibrils.

Variable expression is characteristic for the dominant OI types. Within one OI family with the same basic biochemical defect, a large variation of phenotypes can occur. It is likely that additional gene products influence the phenotypic manifestations of familiar mutations.[93]

It can be concluded that the accumulating data suggest that OI is caused by qualitative and quantitative changes in type I collagen synthesis. OI type I has been shown in a number of cases to result from the decreased synthesis of structural normal collagen. On the other hand, in OI types II and IV, the synthesis of a structurally abnormal collagen occurs in normal amounts, but because of the decreased stability, the total collagen production is reduced. Our knowledge of what is wrong with the collagen molecules produced in OI, is steadily and rapidly increasing, whereas the question of why things subsequently go wrong is far less well understood. This discrepancy is especially evident in families displaying variable phenotypic expression, which is probably due to the modulating effect of connective tissue components other than collagen.
Over the next few years it will be important to clarify genotype-phenotype relationships, to determine how defective molecules function, to determine more of the natural history of different forms of OI, to identify and characterize the genes which modify the effects of the primary mutations and to translate research studies on the molecular basis of OI into information for families and physicians.[94]
In the future new biochemical knowledge on bone and skin collagen from OI patients makes further subdivision on the basis of biochemical characteristics plausible.

B. PURPOSE OF THIS STUDY

The aim of this study was to gain more insight into the nature and the variation in severity of the hearing loss in patients with OI, also in relation to age. Such knowledge is of great significance for career opportunities for people affected by this condition. Also the hearing loss and the results of stapes surgery are subjects of further study.

This is of importance in order to establish the efficacy of stapes replacement surgery with regard to improving the individual patient's hearing.

In 1985, a research project was started, supported by the collaboration between the Ear, Nose and Throat Department of the University Hospital Nijmegen and the Stichting Bio-Kinderrevalidatie (Foundation for paediatric rehabilitation) in Arnhem. The objects of this study were as follows:

1. What is the penetrance of OI type I and what is the expression of the most common features including hearing loss.
2. What is the nature and degree of hearing loss in sufferers of OI type I and how does the hearing loss relate to age.
3. What are the short and long term results of stapes surgery in osteogenesis imperfecta. Is there a relation between surgical findings and results of stapes surgery.
4. Can the results of stapes surgery be predicted with special reference to cases with a poor results of surgery.

C. POPULATION AND METHODS

In the early phase of the study, there appeared to be ample data available at the ENT Department in Nijmegen on osteogenesis imperfecta (type I) patients (including surgical details) and their families. However, when the data were evaluated in the light of the research questions, the population proved to be too small to provide adequate answers to the separate questions. Thanks to the kind cooperation of the Nederlandse Patientenvereniging Osteogenesis Imperfecta (Dutch Society for OI Patients), a large population of osteogenesis imperfecta (type I) patients and their families could be collected, visited and examined. A considerable number of ENT specialists participated in the study by supplying data, which ultimately formed the largest group of osteogenesis imperfecta (type I) patients to date who had undergone stapes surgery. It should be mentioned that part of the data was retrospective and part could be studied prospectively.

Hearing loss has been described in association with every known type of OI. During

the study, it became clear that for the time being, it was only possible to collect sufficient data on patients with OI type I. Therefore, the study questions were not extended to incorporate other types of OI besides type I.

In the early phase of the study, the abnormality was referred to as osteogenesis imperfecta tarda.[95] In the first phase, when the stapes surgery was often studied retrospectively (Chapters 4 to 6),[96-98] the abnormality was described as osteogenesis imperfecta without any further specification of the type, according to the classification of Sillence. In the next phase in which the clinical genetic aspects (Chapter 2)[99] and the relation between the degree of hearing loss and age (Chapter 3)[100] were studied, it was necessary to apply the strict description of osteogenesis imperfecta type I.

For the latter two Chapters, data were required with as little patient selection as possible. Family studies were conducted with the aim of collecting reliable data, so that any possibly unfavourable selection, which may influence the results, would be detected. In this way, we were able to establish in retrospect on clinical genetic and anamnestic grounds that nearly all the patients in Chapters 4 to 6 had osteogenesis imperfecta type I.

More details on the definition of the populations and the methods used are given in the seperate chapters which have been published a seperate entities.

In **Chapter 2**, the penetrance of osteogenesis imperfecta type I and the expression of the most common characteristics are assessed in 30 fully-investigated families with at least two generations of OI sufferers. Distinction is made between families with and without male-to-male inheritance, to exclude an X-dominant pattern of inheritance and genetic imprinting.

In **Chapter 3**, the nature and the degree of hearing loss in patients with osteogenesis imperfecta type I is discussed. In addition, an analysis is made of the influence of age on the degree of hearing loss. The progression of the hearing loss is described on the basis of the clinical genetic study.

In **Chapter 4**, the results of stapes surgery are given for the patients with osteogenesis imperfecta (type I) at the ENT Department of the University Hospital Nijmegen. The hearing thresholds in the pre-operative period as well as the short-term and long-term results are presented together with the surgical findings.

In **Chapter 5**, a review is made of the short-term and long-term results of stapes surgery in osteogenesis imperfecta (type I) for the whole of Holland. A detailed comparison is made with two other studies on short-term and long-term hearing gain.[9,101]

Chapter 6 analyses the initially disappointing-looking results of stapes surgery in patients with osteogenesis imperfecta (type I). A search is made for characteristics which may have predictive value even before surgery. Besides the sex distribution in the study population, the number of fractures, the age at the onset of hearing loss and the age at which stapes surgery took place, various specific characteristics and surgical details are compared to those reported in two other studies and to those reported in a collection of smaller studies we selected from the literature.

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CHAPTER 2

CLINICAL AND GENETIC ASPECTS IN AUTOSOMAL DOMINANT INHERITED OSTEOGENESIS IMPERFECTA TYPE I

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ABSTRACT

In 30 fully investigated family pedigrees in which there were at least two generations of people suffering from osteogenesis imperfecta type I (McKusick no.16620), the data on 144 random offspring could be used for segregation analysis. The major characteristics, blue sclerae, fractures and hearing loss were present in every pedigree. Their penetrance was also calculated.

Precise definitions were used in the study. The segregation ratio was 70:72. The incidence of blue sclerae was 70:70 (100%), for fractures 61:70 (87%) and for hearing loss 30:70 (43%). There was a very clear relationship between age and the progression of the hearing loss.

Dividing the offspring into two groups depending on whether or not male-to-male inheritance was present and performing segregation and penetrance calculation on these data, did not produce any indications that there are two genetically distinguishable subtypes of osteogenesis imperfecta type I. In a smaller group of 107 offspring, calculations could be made on several separate generations.

INTRODUCTION

Over the past ten years, our knowledge on the clinical-genetic aspects of osteogenesis imperfecta (OI) has increased rapidly. The new classification system introduced by Sillence et al.[1] together with the later additions,[2-5] the recent discoveries on the molecular structure of collagen[6] and its biosynthesis,[7-10] has helped to solve many of the mysteries and improve the quality of genetic counseling.

In 1987, it was decided to continue using Sillence's vigilant classification, despite the fact that several questions had remained unanswered, due to of a lack of knowledge on both the biochemical and genetic heterogeneity of the disease.[11]

In this study, segregation and penetrance analyses were performed on a random group of offspring from families with osteogenesis imperfecta type I. We also examined whether a distinction could be made between offspring with and without male-to-male inheritance, to demonstrate the possible existence of two different

genotypes of osteogenesis imperfecta type I.

PATIENTS AND METHODS

For the present study, as much data as possible was collected on patients with osteogenesis imperfecta in the Netherlands. The majority of patients were found to have osteogenesis imperfects type I on the grounds of their anamnesis and physical examination, which showed the presence of the following in the proband and at least two generations of relations: blue sclerae, fractures, hearing loss, hyperlaxibility and other possible characteristics (McKusick no.16620).[12] Classification was not made on the basis of dwarfed growth or curvature of the long bones. There were far less patients with osteogenesis type III (McKusick no.25942) and type IV (McKusick no.16622). None of our patients had ever undergone a diagnostic test, e.g. fibroblast culture, to prove the presence of osteogenesis imperfecta.

In order for the segregation and penetrance analyses to be accurate, it was necessary to prevent several possible forms of patient selection. Therefore, nearly all the offspring in 30 pedigrees of Dutch families with at least two generations of members affected by osteogenesis imperfecta type I were subjected to a clinical examination, whereas for the calculation, the probands were excluded.

The majority of the family members of the propositi were examined by the authors or sufficient data could be obtained. Ultimately, in about 10% of the offspring, we had to rely on data obtained via hetero-anamnesis, because the person in question had emigrated or was deceased. Several offspring were excluded from the analysis: two missed abortions, one abortion whose sex was known, two stillbirths with or without characteristics of the disease.

Members of these families were diagnosed as having osteogenesis imperfecta type I if they had blue sclerae and a history of more than one fracture, whether or not in combination with hearing loss. Especially hearing loss occured in each family.

A number of offspring had never sustained a fracture because of their young age, but on the basis of blue sclerae, a characteristic habitus, a clear family anamnesis and sometimes on the basis of other OI characteristics, they could be diagnosed as having

OI.

The determination of blue sclerae is subjective. We did not use a colour chart, as Sillence et al.[1] In cases where the colour blue was doubtful or the physician had otherwise recorded 'dubious', the sclerae were considered to be normal.

In this study, hearing loss was defined as a mean loss of 15 dB (HL) or more at 0.5, 1 and 2 kHz and/or a mean loss of 30 dB (HL) at 4 and 8 kHz in subjects of up to 50 years of age; in subjects older that 50 years of age (possibly with presbycusis), hearing loss was defined as a mean loss of 20 dB (HL) or more at 0.5, 1 and 2 kHz and/or a mean loss of 35 dB (HL) at 4 and 8 kHz.

We also investigated the hearing loss in the present population using the criteria of two earlier studies.[13,14] Pedersen (1984) considered a hearing threshold of 15 dB at any of the frequencies between 0.25 and 4 kHz to be a hearing loss, whereas Shapiro et al. (1982) applied the same limit to any of the frequencies between 0.25 and 8 kHz. In patients who were found to be hearing impaired but had undergone an ear operation owing to a different disease, the hearing loss was not attributed to osteogenesis imperfecta. Children younger than 6 years of age with otitis media with effusion were considered to have normal hearing. None of the sufferers had to be considered as hearing impaired on the basis of a reliable hetero-anamnesis.

Dentinogenesis imperfecta was not included in this study as a diagnostic characteristic, because in retrospect, it was not possible to establish whether an edentulous patient had suffered from caries or dentinogenesis imperfecta in his or her youth.

For each family pedigree, segregation and penetrance were analysed depending on whether or not male-to-male inheritance was present. They were also calculated for the separate generations in a smaller group of offspring, in which at least two consecutive and complete generations had undergone a thorough clinical examination.

RESULTS

In the total group of 144 offspring from 30 families whose members had been examined thoroughly, 103 (72%) were seen by the authors themselves or had undergone a clinical examination elsewhere at our request (n=25 (17%)) or enough

data were available on them. In 16 cases (11%) we had to make do with data from hetero-anamneses, because 9 of them were deceased, 5 had emigrated and 2 had lost touch with the family and were therefore unreachable.

The group of 144 offspring comprised 79 men and 65 women (group I). Two subgroups were formed depending on whether male-to-male inheritance was present (group II) or absent (group III) (Table 1). Group II comprised 14 families with 78 offspring (47 men and 31 women). Group III comprised 16 families with 66 offspring (32 men and 34 women).

Segregation and penetrance were analysed per generation in 17 families with 107 offspring, in which at least two consecutive generations had been examined thoroughly (Table 2).

Segregation analysis

On the basis of the above-mentioned criteria, 70 offspring (group I) were found to have osteogenesis imperfecta type I. For the cases with male-to-male inheritance (group II) and those without (group III), 40 and 30 were found to have osteogenesis imperfecta type I, respectively. The number of sufferers per decade are shown in Figure 1.

In group I with 70 sufferers, the segregation was 70/72, in group II 40/39 and in group III 30/33. The male:female ratio in the 70 sufferers was 33:37.

In the group where segregation was judged per generation, 51 persons were considered to be OI sufferers, i.e. the segregation was 51/53.5 (Table 2). There was very little difference between the segregation ratios in the first and second generations. In the third generation, only 7 sufferers were present.

Penetrance

Blue sclerae were diagnosed in 79 out of the 144 offspring (group I), of whom 4 by means of hetero-anamnesis. For 9 of these 79 offspring, it was not possible to confirm the diagnosis of OI using the usual criteria.

The penetrance of blue sclerae in group I was 70/70 (100%) (Table 1). Similar penetrance was found in groups II and III. Figure 1 shows the penetrance per decade.

Fractures were observed in 61 of the 144 offspring in group 1 (Table 1). Five healthy

Table 1: Segregation and penetrance analysis in the offspring of families with osteogenesis imperfecta type I*.

Osteogenesis imperfecta type I		Segregation			Penetrance of blue sclerae		Penetrance of fractures		Penetrance of hearing loss	
Offspring		No of Pts	Observed expected ratio	%	No. of Pts	%	No. of Pts	%	No. of Pts	%
I	144	70	70/72	97	70/70	100	61/70	87	30/70	43
II	78	40	40/39	103	40/40	100	35/40	88	18/40	45
III	66	30	30/33	91	30/30	100	26/30	87	12/30	40

* I, total population, II, families with male-to-male inheritance, III, families without male-to-male inheritance.

Table 2: Segregation and penetrance per generation in the offspring of families with osteogenesis imperfecta type I.

	Offspring (n=144)		All generations (n=107)		First generation (n=57)		Second generation (n=40)		Third generation (n=10)	
Osteogenesis imperfecta type I	No of Pts	%	No of Pts	%	No of Pts	%	No. of Pts	%	No. of Pts	%
Segretation	70/72		51/53 5		24/28 5		20/20		7/5	
Penetrance of blue sclerae	70/70	100	51/51	100	24/24	100	20/20	100	7/7	(100)
Penetrance of fractures	61/70	87	46/51	90	24/24	100	18/20	90	4/7	(57)
Pentrance of hearing loss	30/70	43	22/51	43	14/24	58	7/20	35	1/7	(14)

offspring with, as a rule, one fracture in their anamnesis were excluded. The penetrance of fractures in the total population was 61/70 (87%). The distributions in groups I, II and III were similar (Table 2). Figure 1 shows the penetrance per decade. Hearing loss was present in 30 out of the 144 offspring (Table 1). Seven healthy hearing impaired offspring were excluded. The penetrance of hearing loss was 30/70 (43%); the ratios found in groups II and III were very similar. The calculations per generation showed an increase in the penetrance of hearing loss in the older generations (Table 2). Figure 1 shows the penetrance per decade.

When Pedersen's (1984) criteria for hearing loss were applied to our group, we found 33 sufferers out of the 144 offspring, i.e. the penetrance was 33/70 (47%). When Shapiro's (1982) criteria for hearing loss were applied to our group, we found 35 sufferers out of the 144 offspring, i.e. the penetrance was 35/70 (50%).

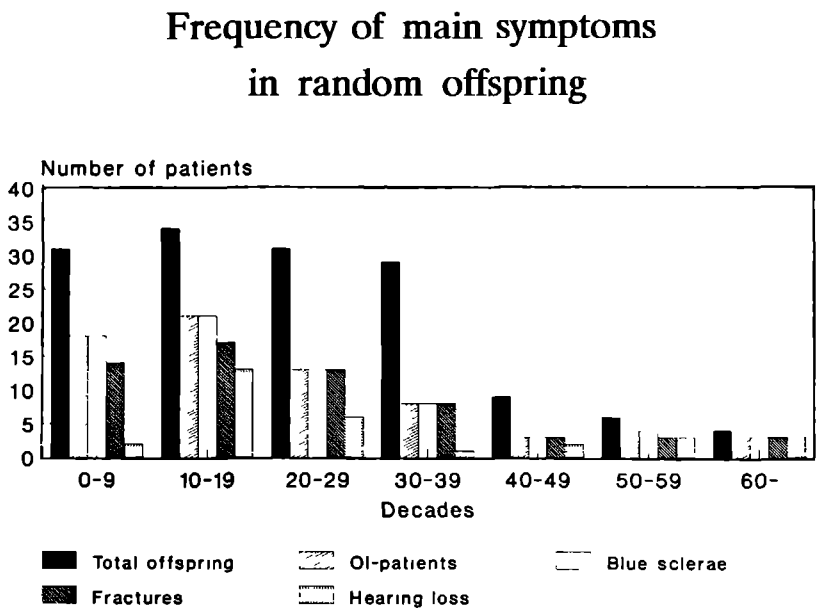

Figure 1: Segregation and penetrance per decade in the 144 random offspring of families with osteogenesis imperfecta type I.

This study on 30 thoroughly examined family pedigrees whose members were suffering from osteogenesis imperfecta type I (McKusick no.16620), comprised 235 family members with 144 random offspring, which offered the opportunity to perform segregation and penetrance analyses. It is peculiar that next to blue sclerae and fractures, also hearing loss occured in each pedigree. For 17 pedigrees, at least two complete generations could be thoroughly examined, and therefore analysis is also presented per generation. These data are of importance for genetic counselling and for later gene-linkage studies.

The three criteria for making a clinical diagnosis of OI proved to be sufficiently reliable in the present study, provided they were clearly defined. Using the criteria separately might lead to overdiagnosis, because none of the three characteristics are specific to osteogenesis imperfecta. Particularly blue sclerae were observed a number of times in healthy offspring and it is obviously possible for nonsufferers to sustain fractures. Hearing loss remains an arbitrary matter: opinions differ as to the extent of hearing loss and the frequencies at which it should be considered abnormal.

The segregation analysis in our random study group produced a ratio of 70:72, which is striking. When the offspring were divided into two subgroups depending on whether male-to-male inheritance was present, no significant shift was observed in the segregation and penetrance analyses. We can therefore conclude on the basis of our findings that in our study population there were no indications of two genetically distinguishable subtypes of osteogenesis imperfecta type I (McKusick no.16620) (Table 1).

In family members in their first decade, we are faced with the risk of overdiagnosis because isolated cases of blue sclerae are fairly common in young children. However, in our study, we applied three criteria for OI diagnosis and thereby excluded this risk.

There were no significant differences between the results of the segregation analyses in the separate generations (Table 2).

For the analysis of the penetrance of the separate characteristics, we used sharply defined criteria. It was striking that neither the fact that the sufferers had blue sclerae nor the presence or absence of male-to-male inheritance had any influence on

penetrance (Table 1). In the total group of offspring, 9 others were found with blue sclerae, but they did not meet the remaining criteria for OI. Overdiagnosis seems to particularly apply to other studies in which blue sclerae was the only criterion.[15,16]

The penetrance of fractures of 61/70 (87%) was a fairly constant factor, which was also found in groups II and III (Table 1) and in the first and second generations (Table 2). Only subjects who had sustained fractures were included; the number and frequency of the fractures were not taken into consideration. These data agreed with those reported in literature, regardless of which definition of fractures was used.[17-19] Age had only a slight influence on the penetrance of fractures. A difference was found between the first two decades (80%) and the other decades (100%), but the difference was small (Figure 1).

The penetrance of hearing loss depended on the criteria used. In this study we chose a mean hearing loss, both for the frequencies 0.5, 1 and 2 kHZ and for 4 and 8 kHz. In addition, the threshold was raised for subjects older than 50 years of age. The penetrance of 30/70 (43%) was similar in groups II and III (Table 1). In the second decade, the penetrance of hearing loss increased, which shows that age plays a role in the progression of hearing loss (Figure 1). The increase in this penetrance value per generation makes it likely that penetrance increases with age (Table 2). We can also assume that after the third decade, the majority of sufferers who will ever be confronted with (invalidating) hearing loss, will have been recognised. The data in Figure 2, which were compiled on the basis of mean hearing thresholds for the frequencies 0.5, 1 and 2 kHz in all sufferers, show that after the third decade, very few ears had normal hearing thresholds.

In order to find out how much Shapiro's (1982) and Pedersen's (1984) definitions of hearing loss would affect our findings, we applied their definitions to our data. Using Pedersen's definition for the penetrance of hearing loss, our ratio increased from 30/70 (43%) to 33/70 (47%); using Shapiro's definition the penetrance was 35/70 (50%). Contrary to the present study, in which a hearing loss was defined by means of mean values at various frequencies between 0.5 and 8 kHz, the other studies applied a definition of hearing loss in which only one frequency was stated and only one of the studies (Shapiro et al.,1982) included a frequency of 8 kHz. When we applied these two factors to our random Dutch study population, only a slight increase in the

penetrance of hearing loss was observed. Therefore, the effect of the various definitions was only very slight.

Figure 2 shows the extent of hearing loss in our large random Dutch study population. It is striking that a considerable hearing loss was already present in the second decade.

Further studies and presentations on the relationship between the extent of hearing loss and the penetrance may provide useful information and identify indicators which can predict the progression of the hearing loss in individual cases.

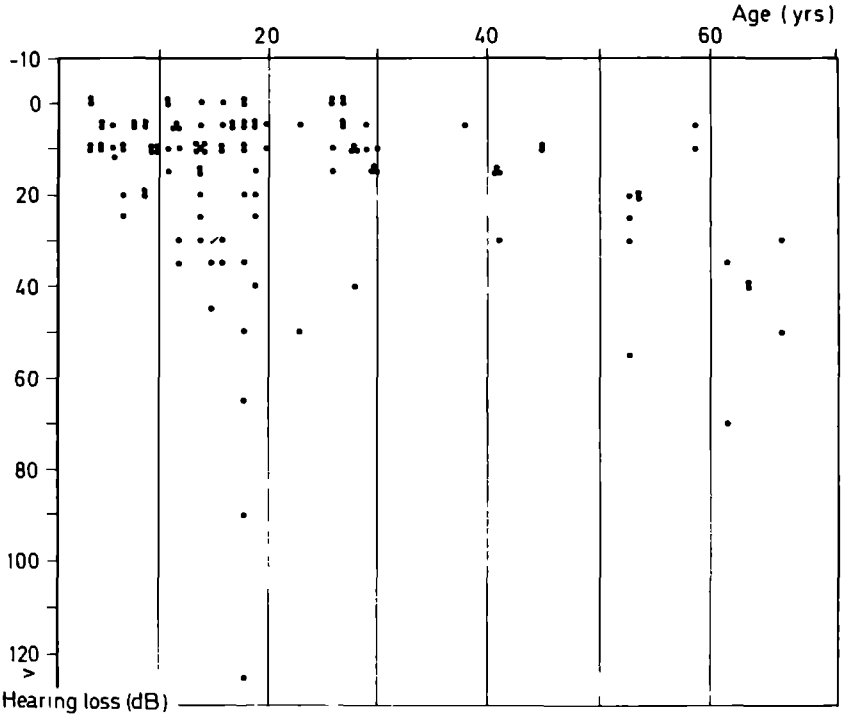

Figure 2: Plot diagram of the mean hearing thresholds of the Fletcher index (0.5, 1, and 2 kHz) of both ears from 70 random osteogenesis imperfecta type I sufferers against age, per decade.

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CHAPTER 3

HEARING LOSS IN RELATION TO AGE IN OSTEOGENESIS IMPERFECTA TYPE I

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ABSTRACT

Hearing loss was studied in relation to age in 142 subjects suffering with osteogenesis imperfecta type I. In order to estimate any selection these subjects were compared to a random subsample of 70 subjects with the same disease. It appeared that in the group of 142 subjects, particularly below the age of 30 years, considerable selection had occurred on hearing loss.

The hearing threshold increased gradually with age. A hearing loss greater than 30dB was observed for 51% of the subjects older than 20 years and younger than 60 years. The median hearing loss increased from the 10th to the 45th year of life with an average of about 1dB/year at the frequencies 0.5-4kHz and an average of 1.7dB/year at 8kHz. The sensorineural component of the hearing loss showed an average annual increase of 0.6dB (0.5-4kHz) up to 1.3dB (8kHz); the average annual increase in the conductive component of the hearing loss appeared to be 0.4dB at all frequencies. The sensorineural component was the major component in severe hearing loss.

INTRODUCTION

Over the past three decades, hearing loss has been reported as a major symptom of osteogenesis imperfecta.[1-13] A variety of definitions of hearing loss and examination methods can be found in these reports.[7-10,12,13] The groups of affected subjects examined do not usually represent random samples.

Despite the frequently described progression of hearing loss with age, age has seldom been taken into account in the analyses of hearing loss caused by osteogenesis imperfecta. Obviously the progression and the extent of hearing loss heavily depends on the age of the affected subjects. The type of hearing loss may be conductive, sensorineural or mixed.

The present study analyzes the type and extent of hearing loss related to age in a selected sample of 142 subjects affected by the autosomal dominant type I of osteogenesis imperfecta.[14] The results are compared to those of a previous study on a random sample of 70 affected subjects, who also had osteogenesis imperfecta type I,

from fully examined sibships.[13]

PATIENTS AND METHODS

With the assistance of a number of Dutch ENT surgeons and the Dutch Association of Patients with Osteogenesis Imperfecta, we were able to compile a series of 142 subjects affected with osteogenesis imperfecta type I for this study. The clinical diagnosis was based on the medical history and clinical examination. Previous reports concerned the findings and the results of ear surgery in subsamples of the present series.[15-17] The penetrance of hearing loss was studied in a random subsample of 70 affected subjects, established by fully examining the sibships in 30 families with at least one affected subject in 2 generations.[13] Only 60 of these 70 patients had undergone clinical audiometry. Of the other 10 patients, 2 were deceased, 6 were too young and 2 were living abroad. None of the latter 10 patients were known as hard-of-hearing.

Pure tone auditory thresholds (decibels hearing level) were obtained (from non-operated ears) under standard conditions in a soundproof room at our clinic or elsewhere. Subjects younger than 4 years of age were excluded from this study. Also excluded were subjects with hearing loss that could be attributed to causes other than osteogenesis imperfecta, such as chronic otitis media. When several audiograms were available which had been measured at different ages, we took the one obtained at the youngest age. We used the following working definitions for the various types of hearing loss paralleling the definitions given by Shapiro et al.[9] and Pedersen.[10]

1. Conductive loss: average air-bone gap for the frequencies 0.5, 1 and 2kHz or else the average air-bone gap at 4 and 8kHz greater than 15dB; corresponding bone conduction threshold below 15dB.
2. Sensorineural loss: average air conduction threshold equal to or greater than 15dB at the frequencies as indicated above; corresponding air-bone gap smaller than 15dB.
3. Mixed loss: average air-bone gap equal to or greater than 15dB at the frequencies as indicated above; corresponding bone conduction threshold equal to or greater than 15dB.

The synopsis on hearing loss and age presented in Tables 1 and 2 provides a comparison to the relevant literature.[1-3,5-10,12,13,18] The different types of hearing loss are shown in two age classes (Table 3). Detailed cross-tables (hearing loss by age) were composed for the present group of 142 subjects (Table 4) and the previously reported random subsample of 70 subjects belonging to the fully examined sibships, who were not selected for their hearing loss (Table 5),[13] in order to make a direct comparison.

The statistical test used was the chi-square test for a 2 x 2 table, with the level of significance of $p=0.05$ (X^2 value 3.84). Scatter plots were prepared for the data on hearing loss and age; details about the type of threshold data and the analyses involved are given where relevant.

RESULTS

The proportion of affected subjects having hearing loss and relevant data from the literature are presented in Table 1. The present study relates to the highest percentage (78%) of hearing loss reported so far. The exact application of the definitions of hearing loss given by Pedersen[10] and Shapiro[9] yielded 80% and 83% hearing loss, respectively, for the present series, which indicates that there are only slight differences between the definitions. The random (sub)sample reported by Garretsen & Cremers[13] yielded a much lower percentage (43%) of hearing loss.

It is remarkable that the family studies[1-3,5-8] yielded a similar low percentage (90 of 212 patients, or 42%). The latter studies, including the work by Garretsen & Cremers,[13] indicate a mean percentage of 43% for hearing loss, which has a corresponding proportion of 120/282. This differs significantly from the other non-family studies,[9,10,12,18] for whom 502 of 769 patients (65%) are hard of hearing. Table 2 shows the relation between the proportion of subjects with hearing loss among the affected subjects and the age of the subjects (in decades) for the present and some other relevant studies.[5,7-10,12,13] For those below 30 years of age, hearing loss was observed for 96/268, or 36%. The present study, however, had a significantly higher proportion of subjects with hearing loss (54/82, or 66%). For those aged 30 years and

Table 1: Survey of studies on hearing loss in osteogenesis imperfecta.

Author(s) Reference	Year	No of Pts	Limited to OI type I	Definition of hearing loss	Clinical Audiometry	Hearing loss related to age	Random population	Proportion of patients with hearing loss	(%)
Bell[18]	1928	346	-	-	-	-	-	228/346	(66)
Stoller[1]	1962	26	+	-	unknown	-	one family	11/26	(42)
Carey et al.[2]	1968	23	+	-	unknown	-	one family	10/23	(43)
Dufour & Bertrand[3]	1972	11	+	-	unknown	-	one family	4/11	(36)
Carruth et al[5]	1978	10	+	-	+	+	- (3 Fam)	5/10	(50)
Quisling et al[6]	1979	68	+	-	+ and portable	-	- (1 Fam)	20/42	(47)
Riedner et al.[7]	1980	70	-	+	+ and portable	+ (in decades)	- (13 Fam)	29/70	(41)
Cox & Simmons[8]	1982	30	-	+	only portable	+ (in decades)	- (5 Fam)	11/30	(37)
Shapiro et al[9]	1982	55	-	+	+	+ (+/- 30 yrs)	-	35/55	(64)
Pedersen[10]	1984	173	-	+	+ and portable	+ (in decades)	- (75% Pop.)	97/173	(56)
Stewart & O'Reilly[12]	1989	56	-	+	+ and portable	+ (in decades)	-	31/53	(58)
Garretsen & Cremers[13]	1991	70	+	+	+	+ (in decades)	+	30/70	(43)
This study		142	+	+	+	+ (in decades)	-	111/142	(78)

Note: The proportion of patients with hearing loss is presented with the percentage in parentheses. The definitions of hearing loss may differ.
"Portable" means portable equipment and implies less accuracy than usual.
"75% Pop." refers to 75% of the Danish population.

Table 2: Survey of studies on hearing loss in osteogenesis imperfecta as dependent on age (in decades).

Author(s) Reference Year	Definition of hearing loss	Number of OI-pts	Mean age (range)	Age (yrs)								
				0-9 (%)	10-19 (%)	20-29 (%)	< 30 (%)	30-39 (%)	40-49 (%)	50-59 (%)	60-69 (%)	≥ 30 (%)
Carruth[5] 1978	-	10	44 (8-77)	0/1	0/1		0/2	1/3	0/1	1/1	3/3	5/8 (62)
Riedner[7] 1980	+	70	-	0/10(0)	3/8 (38)	6/19 (32)	9/37(24)	2/9 (22)	4/8 (50)	7/9 (78)	7/7 (100)	20/33 (61)
Cox & Simmons[8] 1982	+	30	20 (4-67)	1/8 (13)	4/10 (40)	2/5 (50)	7/23(30)	1/3	2/3		1/1	4/7 (57)
Shapiro[9] 1982*	+	55	- (2-64)				18/37(49)					17/18 (94)
Pedersen[10] 1984**	+	173	-	5/23(22)	10/36 (28)	18/31 (58)	33/90(37)	15/29(52)	12/21 (57)	8/12 (67)	20/21 (95)	64/83 (77)
Stewart & O'Reilly[12] 1989	+	53	- (10-60)		2/13 (15)	6/14 (43)	8/27(30)	5/7 (71)	11/12 (92)	7/7 (100)		23/26 (88)
Garretsen & Cremers[13] 1991	+	70	22 (4-66)	2/18(11)	13/21 (62)	6/13 (46)	21/52(40)	1/8 (13)	2/3	3/4	3/3	9/18 (50)
This study	+	142	27 (4-87)	4/13(31)	24/38 (63)	26/31 (84)	54/82(66)	23/24(96)	17/18 (94)	9/10 (90)	8/ 8 (100)	57/60 (95)

Note: The proportion of patients with hearing loss within a given age-class is presented.
Percentage in parentheses (only for n>4).
* Original classes 1st - 3rd decades and 4th - 7th decades.
** Interpretated from the original figures.

older, the present study and the one by Shapiro et al.[9] had higher proportions of hearing loss (57/60 or 95%, and 17/18 or 94%, respectively) than the other selected groups of patients,[10,12] which showed an average proportion of 87/109 (80%). The proportions corresponding with 94-95% are significantly higher than those for all the family studies[5,7,8,13] taken together, which yielded a proportion of subjects with hearing loss of only 38/66 (58%). The data in Table 2 clearly show that the proportion of subjects with hearing loss increases with age. This is particularly clear in the larger series. An exception is the series published by Garretsen & Cremers,[13] which showed large deviations from the general trend in the 2nd and the 4th decades. Together with the present series, of which it represents a subsample, the series by Garretsen & Cremers[13] differs significantly from the others in the high proportion of hearing loss in affected subjects in their second decade of life.

The statistics for normal hearing and the various types of hearing loss are presented in Table 3, including two age classes. Normal hearing was most frequent at a younger age. Conductive loss was found only in a few young affected subjects. Mixed hearing loss was the most frequent type of hearing loss and the frequency increased significantly with age. Constant proportions, independent of age, were found for sensorineural hearing loss, Shapiro's CHOI[9] and deafness.

Table 3: Type of hearing loss in 142 patients with osteogenesis imperfecta type I.

Age (yrs)	<30	30 or more	Total
Normal hearing	52 (34)	8 (6)	60 (21)
Conductive hearing loss	3 (2)	0	3 (1)
Mixed hearing loss	56 (37)	89 (68)	145 (51)
Sensorineural hearing loss	27 (18)	25 (19)	52 (18)
CHOI*	10 (7)	7 (5)	17 (6)
Deaf	3 (2)	2 (2)	5 (2)
Total	151 (100)	131 (100)	282** (100)

Note: Percentage in parentheses
* Hearing loss characteristic for OI (CHOI) according to Shapiro et al.[9]
** Data not apllicable for one ear in two cases

Table 4 is a cross-table of air conduction thresholds by age (in decades) for the proportion of ears with a given hearing loss in the present series of selected subjects. Table 5 is a similar table for the random subsample.[13] In Tables 4 and 5, the median hearing loss per decade is also presented. In the present selected sample, the median hearing loss increased from the 1st decade from 0-10dB up to about 30dB in the 3rd decade (Table 4). In the random sample (Table 5), the median hearing loss only increased after the fourth decade. In the selected sample the air conduction threshold was higher than 30dB for (85/166) 51% of the affected subjects 20-59 years of age (Table 4); a further (significant) increase in this proportion could only be noted in the seventh decade. Testing the proportions in the cells for 0-10dB and the second or third decade in the random sample (Table 5) against the corresponding proportions in the selected sample (Table 4) showed that the random sample had significantly higher proportions in these cells (pertaining to 58% as compared to 47% and to 70% compared to 27%, respectively, see Tables 4 and 5).

Table 4: Hearing thresholds in 142 patients with osteogenesis imperfecta type I.

Age (yrs)	4-9	10-19	20-29	30-39	40-49	50-59	60-69
Hearing loss							
0-10 dB	21/26 (81)	36/76 (47)	16/60 (27)	6/50 (12)	10/36 (28)	5/20 (25)	
15-30 dB	5/26 (19)	14/76 (18)	14/60 (23)	12/50 (24)	9/36 (25)	8/20 (40)	3/16 (19)
35-50 dB		16/76 (21)	21/60 (35)	12/50 (24)	5/36 (14)	1/20 (5)	7/16 (44)
55-90 dB		8/76 (11)	6/60 (10)	17/50 (34)	9/36 (25)	3/20 (15)	5/16 (31)
95 dB or more		1/76 (1)	3/60 (5)	2/50 (4)	3/36 (8)	3/20 (15)	1/16 (6)
more than 30 dB	0/26 (0)	25/76 (33)	30/60 (50)	31/50 (62)	17/36 (47)	7/20 (35)	13/16 (81)

Note: Proportion of 284 ears within a given class of hearing loss (dB HL, Fletcher-index) in decades
Percentage in parentheses
The shading indicates the median hearing loss per age class

The difference in the relationship between the air conduction threshold and age between the two series (random and selected cases) appeared to be significant. With increasing age, the two series tended to develop a similar (median) hearing loss, but the series of selected cases showed selection especially at a younger age. For each pair of corresponding cells in Tables 4 and 5, we calculated the difference between the random and the selected samples. In this way we obtained a two-dimensional distribution which showed a surplus in proportion compared to the random sample (Table 5) in the following cells: 35-50dB/10-19yrs (9/24 or 38%); 55-90dB/10-19yrs (6/24 or 25%); 35-50dB/20-29yrs (19/40 or 48%). For the three cells combined, the difference distribution indicated a proportion of 34/64 (53%), while this combination for the random sample (Table 5) yielded a proportion of only 11/72 (15%); the difference is significant. The difference distribution had a median threshold for all age classes beyond the first decade which coincided almost invariably with the class 35-50dB.

Table 5: Hearing thresholds in 70 patients with osteogenesis imperfecta type I.

Age (yrs)	4-9	10-19	20-29	30-39	40-49	50-59	60-69
Hearing loss							
0-10 dB	20/24 (83)	30/52 (58)	14/20 (70)	2/ 2	2/ 6 (33)	2/ 8 (25)	
15-30 dB	4/24 (17)	12/52 (23)	4/20 (20)		4/ 6 (67)	5/ 8 (63)	1/ 6 (17)
35-50 dB		7/52 (13)	2/20 (10)				4/ 6 (67)
55-90 dB		2/52 (4)				1/ 8 (13)	1/ 6 (17)
95 dB or more		1/52 (2)					

Note: Proportion of 118 ears within a given class of hearing loss (dB HL, Fletcher-index) in decades
Percentage in parentheses (only for n>4)
The shading indicates the median hearing loss per age class.

In order to establish further characteristics of the hearing loss as it develops with age, we prepared separate scatter plots for the present series, for air conduction, bone conduction and air-bone gap at all the frequencies. Those for the mean hearing loss at 0.5, 1 and 2kHz are depicted in Figures 1 through 3.

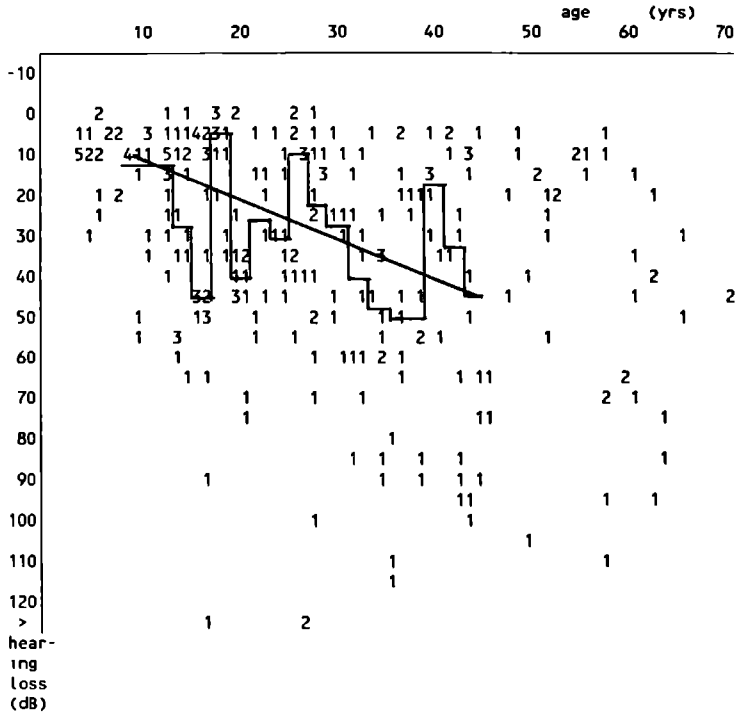

Figure 1: The mean air conduction threshold (dB HL, Fletcher Index) in the selected group (282 ears) plotted against age (years).

Note: The numbers in the figure (n<10) correspond with the number of ears with a given combination of a certain hearing loss and age at the appropriate coordinates. The histogram-like contour represents the interconnected median values for hearing for age classes (width 2 years) covering 10-45 years of age (10-11, 12-13, ., 42-43, 44-45 years)
The linear "regression" of this "biennial" median hearing loss on age has been visually estimated and the resulted regression line is drawn (continuous sloped line). It indicates the general trend from 10 dB at 10 years towards 45 dB at 45 years.

In the plots we have indicated the median hearing loss (class width 2 years in order to obtain n>4 for a reliable estimation of the median). It can be seen from Figures 1 through 3 that we utilized the median values to estimate the linear "regression" of hearing loss on age (continuous sloped line). It should be noted that this "regression analysis" was limited to the age range 10-45 years for the following reasons:

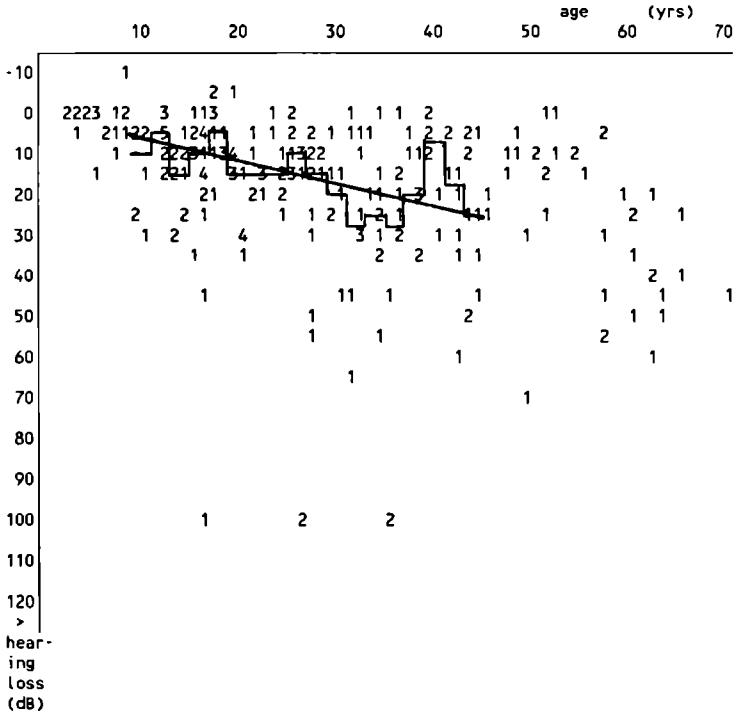

Figure 2: The mean bone conduction threshold (dB HL, Fletcher Index) in the selected group (282 ears) plotted against age (years).

Note: See fig. 1 for legend.
The regression line indicates the general trend from 5 dB at 10 years towards 25 dB at 45 years.

1. In the age groups younger than 10 years and older than 45 years of age, there were relatively few data available, especially regarding bone conduction and air-bone gap, i.e. a class width >2 years would be required in order to obtain n>4;
2. This particular age range showed the most prominent increase in hearing loss;
3. The distributions of the air and bone conduction thresholds at 4 and 8kHz, particularly in the older patients, appeared to be bimodal, analogous to otosclerosis,[19] which would complicate a meaningful analysis.

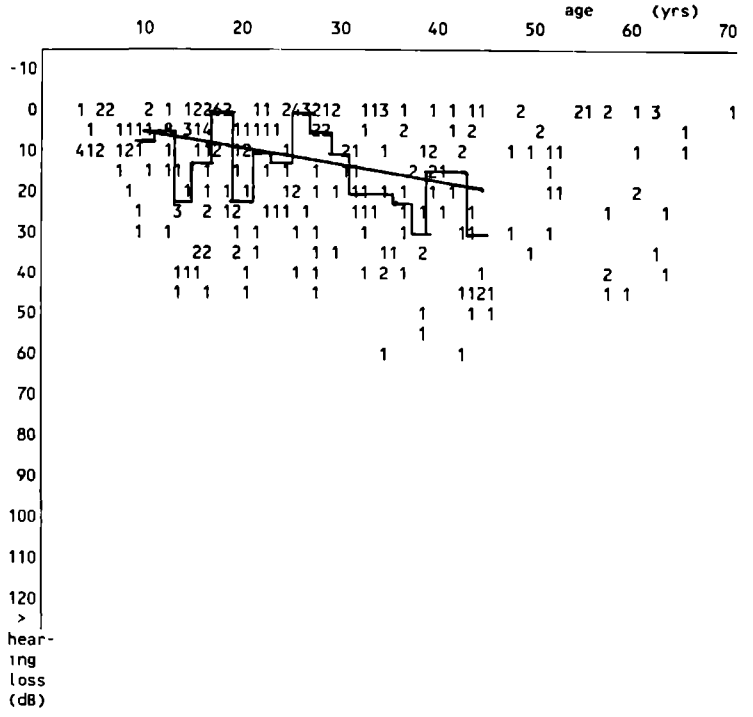

Figure 3: The mean air-bone gap (dB HL, Fletcher index) in the selected group (282 ears) plotted against age (years).

Note: See fig. 1 for legend.
The regression line indicates the general trend from 5 dB at 10 years towards 20 dB at 45 years.

The results of the analysis are presented in Table 6 and yields the following results for the selected group.

1. The sensorineural component of hearing loss increased with both age and frequency;
2. The conduction component increased with age, to a similar degree for all frequencies;
3. The major increase in hearing loss was invariably shown by the sensorineural component: 0.6dB/yr for the mean of 0.5, 1 and 2kHz, 0 7dB/yr at 4kHz and 1.3dB/yr at 8kHz. The increase in air-bone gap with age was limited to about 0.4dB/yr.

Table 6: Median hearing loss and progression of hearing loss in 142 patients with osteogenesis imperfecta type I.

	Median hearing loss (dB HL)		Progression (dB/yr)
Age	10 yrs	45 yrs	
0.5, 1, 2 kHz			
Bone conduction	5	25	20/35 = 0 6
Air-bone gap	5	20	15/35 = 0 4
Air conduction	10	45	35/35 = 1
4 kHz			
Bone conduction	5	30	25/35 = 0 7
Air-bone gap	5	20	15/35 = 0 4
Air conduction	10	50	40/35 = 1 1
8 kHz			
Bone conduction	5	50	45/35 = 1 3
Air-bone gap	5	20	15/35 = 0 4
Air conduction	10	70	60/35 = 1 7

Note Median hearing loss (dB HL) for 142 selected patients with osteogenesis imperfecta type I at the age of 10 and 45 years, for the mean at 0 5, 1 and 2kHz, for 4kHz, and for 8kHz, for air conduction, bone conduction and air bone gap, together with the calculated progression (dB/yr)

The present report on a group of 142 selected subjects with osteogenesis imperfecta type I shows the highest proportion of hearing loss reported so far. A comparison with the random sample,[13] which formed part of this series, showed that considerable selection on hearing loss had taken place at a rather young age. It is interesting to see that the median hearing loss of the distribution of the difference between the selected and the random samples, i.e., which relates to the group of affected subjects who were selected for ear surgery because of their hearing loss, coincides with the class of 30-50dB loss in air conduction threshold at any age from 10 years onwards. Apparently, the presumed selection has taken into account that a Fletcher index of more than 30dB renders the hearing capacity socially ineffective.

The findings relating to Table 1 suggest the possibility that the family studies concern series of patients which are more similar to a random sample than to a selected sample. Therefore, it seems justified to consider the prevalence of hearing loss in osteogenesis imperfecta type I as being 43%. It appears from Table 2 that the series with selected patients distinguish themselves especially by a greater hearing loss at an increasing age (30 years and older). In the present series, the proportion of subjects with hearing loss was higher than in any other series published so far, also at a younger age. It may be relevant that the "self-selection" of affected subjects with hearing loss played a role, because a patient association lent its active support to the present study.

When comparing the present selected sample (Table 3) to other selected samples, as far as possible, as regards the type of hearing loss, the present series included more cases of mixed hearing loss, especially in the older patients, than the series published by Shapiro et al.[9] and Pedersen.[10] The present series also showed considerably more sensorineural loss (only) at a young age as compared to Shapiro et al.[9] and Pedersen.[10] This only holds true as regards the comparison with Shapiro et al.[9] if CHOI is set apart. This type of hearing loss, that was found by these authors in both the lower and higher age groups in 47% of the ears, was only found in a minor percentage by us (Table 3), as well as by Pedersen.[10] Others have also found that the predominant type of hearing impairment in osteogenesis imperfecta was the mixed type, although to a much lesser degree than in the present study.[5,7,8,12] Stewart & O'Reilly[12] and Riedner et al.[7] indicated that conductive loss, as far as it was present,

prevailed in the younger age group. Stewart & O'Reilly,[12] just as we did, described an age-independent proportion for the sensorineural type of hearing loss.

The present series showed gradual progression in hearing loss with age. A considerable increase in the hearing loss took place especially from the 10th to the 45th year of life, which comprised a considerable increase in sensorineural hearing loss and only a limited increase in conductive loss (Table 6). We studied individual follow-up data covering 2 through 24 years (average 9.6 years) on all the subjects who had ear surgery.[16] Between 1 and the average 9.6 years after operation, the mean hearing level in the operated ear dropped by 6.5dB, which almost equals the indication given in Table 6, despite the fact that the conductive component in postoperative hearing loss plays a lesser role. Also the non-operated ear showed a similar progression in hearing loss.[16]

It was intriguing to see that the increase in air-bone gap seemed to be limited to about 0.4dB/yr, independent of the sound frequency.

Less than 50% of the affected subjects older than 20 years of age had averages of 30 dB (Fletcher index) or better, also called "social hearing". From two previous reports[15,16] it appeared that among 58 operated ears, there was only one ear with social hearing, preoperatively. Postoperatively, 24 ears (41%) did not reach the level of social hearing. The above evaluated progression of hearing loss with age, as already stipulated, occured in both the non-operated and the operated ear and to a similar degree.[17] The average hearing gain immediately after the operation was about 24dB (see Garretsen & Cremers,[16] Table 4), thus, given the progression in hearing loss such as presented in Table 6, the hearing gain tends to "disappear" after a follow-up interval of several decades, as indeed seemed to be the case in the patients with a long enough follow-up. In addition, it should be realised that the patients have an artificial sound transmission mechanism after the operation and that the postoperative hearing gain is mainly of the conductive type. Therefore, the expected yearly conductive hearing loss of 0.4dB does not apply anymore to operated ears. In this way, on the one hand, the postoperative hearing gain will remain intact over a period which is longer than the period on analogy with a deterioration of 1dB/yr. On the other hand, however, the progression of sensorineural hearing loss of operated patients may be more than in non-operated patients. From an earlier study it became clear that a relatively greater preoperative sensorineural hearing loss was present particularly in the patients who were operated on at a young age.[17] It is possible that

in this group of patients, the progression of sensorineural hearing loss which occurs pre- and postoperatively is greater than in the average patient.

It seems justified to advise the affected subjects to avoid, if possible, the choice of a type of profession which depends heavily on auditory communication.

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CHAPTER 4

STAPES SURGERY IN OSTEOGENESIS IMPERFECTA

C.W.R.J.Cremers and A.J.T.M.Garretsen

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ABSTRACT

Between 1968 and 1986 stapes surgery has been performed in the Nijmegen University Department of Otorhinolaryngology in 11 patients (14 ears) with osteogenesis imperfecta. Detailed information about pre- and postoperative hearing levels, findings at surgery, and the follow-up period are presented. In most cases the stapedectomy has been successful.

INTRODUCTION

In 1917 Van der Hoeve and De Kleyn from the Netherlands were the first to report hearing loss in several members of a family with osteogenesis imperfecta.[1] The relationship between blue sclerae and brittle bones had been noted for the first time a few years previously. Osteogenesis imperfecta forms a group of diseases with an anomaly in collagen synthesis, well known because of the brittle bones. Recently, 4 major forms of osteogenesis imperfecta have been recorgnized, which have been further subdivided. Autosomal dominant and autosomal recessive patterns of inheritance are possible.[2-4] Shapiro et al[5] mentioned that a hearing loss, most frequently sensorineural, occurred in 49% (younger than 30 years) and 94% (older than 30 years) of patients with osteogenesis imperfecta.

A distinct sensorineural hearing loss at 6 and 8 kHz has recently been reported as a new additional feature.[5] The hearing loss is mostly small and can be located in the middle ear, the inner ear or both. For a long time osteogenesis imperfecta was considered to be a more serious form of otosclerosis. This concept has been proved to be incorrect. Stapes surgery in osteogenesis imperfecta has been considered to be more risky than in otosclerosis.

PATIENTS AND METHODS

In the period 1968 to 1986 11 patients with osteogenesis imperfecta underwent stapes

surgery in the Nijmegen University Department of Otorhinolaryngology; in three patients surgery was bilateral. In all 14 ears, the stapes was replaced by an all-teflon 0.6 mm or a teflon-wire 0.4 mm prosthesis. The pre- and postoperative hearing level and the hearing gain are presented separately for each ear in Figure 1.a and 1.b. The time of the follow-up is noted separately. No revision surgery has been performed in these ears.

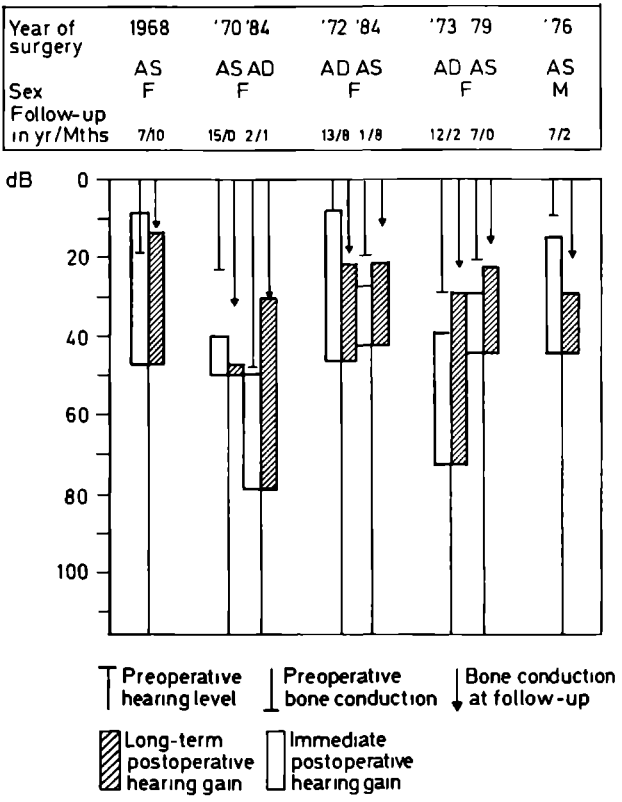

Figure 1.a: Results of 14 stapedectomies in osteogenesis imperfecta in terms of the average pure-tone threshold (in dB, HL) for the frequencies 0.5, 1, and 2 kHz. AD indicates right ear; AS, left ear.

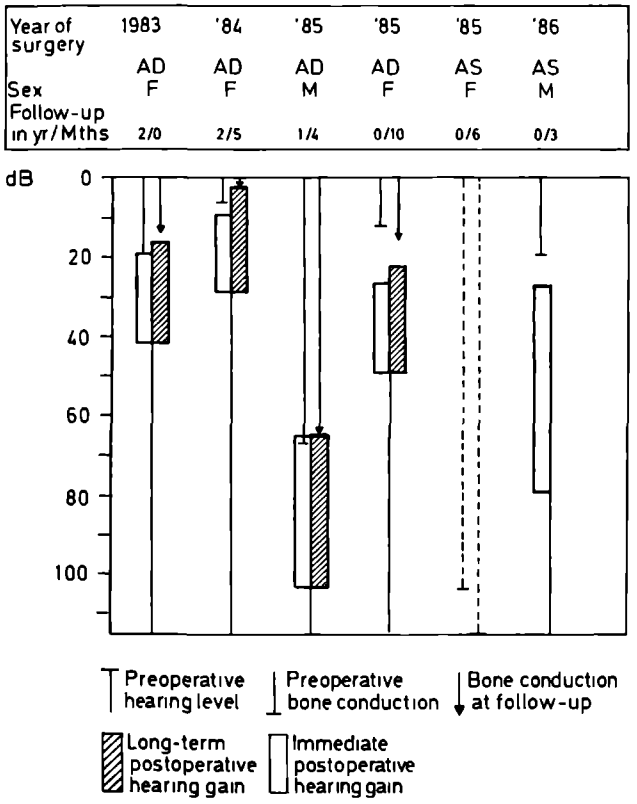

Figure 1.b: Results of 14 stapedectomies in osteogenesis imperfecta in terms of the average pure-tone threshold (in dB, HL) for the frequencies 0.5, 1, and 2 kHz. AD indicates right ear; as, left ear.

RESULTS

Fractured stapes crura were seen in three ears and atrophy of the stapes crura in another three ears (Table 1). Disturbing hemorrhage of the mucosa and/or stapes footplate was noted in six ears. In all of these ears, the footplate was found to be fixed. Thick brittle footplates were seen in 10 ears.

Table 1: Findings during stapes surgery in 14 ears from 11 patients with osteogenesis imperfecta.

Findings at operation	No. of ears	%
Footplate		
Fixed	14	100
Thick and brittle	10	71
Bleeding	2	14
Stapes crura		
Fractured	3	21
Atrophic	3	21
Mucosa		
Bleeding	6	43

The air-bone gap was closed to within 10 dB in 12 of the 14 ears. It is striking that in 5 of these 12 successfully operated ears an air-bone gap of 10 dB was achieved. It is an open question whether these small air-bone gaps distinguish this disease from otosclerosis. The case operated in 1968 has an air-bone gap of 15 dB. A recent case with bilateral, almost total deafness did not improve after stapes surgery. Dizziness after surgery was only a temporary complication.

DISCUSSION

About 50% of the persons with osteogenesis imperfecta will experience a hearing loss during their lives. This hearing loss is progressive. There can be a conductive and a sensorineural component. This hearing loss can be so progressive that it can result in total deafness. Since many of these patients are already more or less handicapped by their disease, the otologist's major concern may therefore be an improvement of their hearing. Since in the past, osteogenesis imperfecta was considered to be a more serious form of otosclerosis, fear of complications led to some hesitation to embark upon stapes surgery.

After the period that fenestration of the lateral semicircular canal had been performed, the first report of a succesfull stapedectomy in osteogenesis imperfecta was given by Sooy in 1960. Since then a series of reports on stapes surgery in osteogenesis imperfecta have been published.[6-19] Most of these reports concerned case reports or small series. In the late seventies the first reports on 10 stapedectomies or more have been published.[12-17] Previous reports on dead ears after stapedectomy had been published in small series by several authors.[9-11] Brosnan et al[12] described one dead ear after 10 stapedectomies. Shea and Postma[14] reported a complete sensorineural hearing loss for 2 out of 24 cases with long-term results (11%). Of the 51 cases with a one year follow-up only these two had a decrease in their hearing (4%). Pedersen and Elbrønd[13,15] reported no dead ears after stapedectomy in 43 ears. Our series of 14 stapedectomies also did not show any increased postoperative sensorineural hearing loss. One of our patients experienced a progressive deafness over several decades resulting in complete deafness of one ear and almost complete deafness of her best ear. Stapedectomy has not been successful in improving her hearing.

We preferred to present our results the way Pedersen and Elbrønd[13,15] presented theirs. By using this method detailed information can be given in a few tables for each ear of larger series. The results of Shea and Postma,[14] Pedersen and Elbrønd,[13,15] and our own results show that a small air-bone of about 10-15 dB for 500-2,000 HZ postoperatively is not so unusual. The air-bone gap was closed in our series to within 10 dB in 12 of the 14 ears. It is striking that in 5 of these 12 successfully operated ears an air-bone gap of 10 dB was achieved. The question remains whether these small air-bone gaps distinguish this disease from otosclerosis.

Our study supports the concept that osteogenesis imperfecta is clinically different from otosclerosis. Considering these results we conclude that surgical intervention for the conductive hearing loss in osteogenesis imperfecta is a reasonable alternative to amplification. Although the surgical results in osteogenesis imperfecta are good, they are possibly not as good as in otosclerosis.

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CHAPTER 5

EAR SURGERY IN OSTEOGENESIS IMPERFECTA CLINICAL FINDINGS AND SHORT-TERM AND LONG-TERM RESULTS

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ABSTRACT

Preoperative and postoperative hearing results and long-term results of stapedectomy have been investigated in 58 ears (47 patients) with osteogenesis imperfecta.
After 3 months hearing gain had been achieved in 49 (85%) of 58 ears.
Twenty-seven (68%) of 40 ears followed up for an average of 9.6 years (range, 2 to 24 years) had no deterioration of their immediate postoperative hearing gain.
In the other ears, the decrease in hearing gain in the long term was due to progression of the sensorineural component of the hearing loss. Complete closure of the air-bone gap remained unchanged in 26 (70%) of 37 ears.
In 6 (10%) of 58 ears the sensorineural component of the hearing loss increased as an immediate result of the operation.
In 5 other ears (9%) progressive sensorineural hearing loss was seen only after more than one year. A natural course of the disease is assumed as the cause because progressive sensorineural hearing loss has also been seen in the non-operated contralateral ears of these patients.

INTRODUCTION

Osteogenesis imperfecta forms a group of diseases with an anomaly in collagen synthesis. This disease is renowned because of brittle bones. Recently, four major forms of osteogenesis imperfecta have been recognised and have been further sub-divided.[1-3] Autosomal dominant and autosomal recessive patterns of inheritance are possible. The autosomal dominant inherited type I, formerly also called osteogenesis imperfecta tarda, is the most frequent. In 1917 Van der Hoeve and De Kleyn[4], from the Netherlands, were the first to report hearing loss in several members of a family with osteogenesis imperfecta tarda, with an autosomal dominant pattern of inheritance. Independently in 1917, Bronson[5] also reported the same triad of blue sclerae, brittle bones, and hearing loss in 19 cases. Shortly thereafter, the British otologist Fraser[6] examined these 19 patients and concluded in 1919 that there was a conductive hearing loss in some of these patients. The promontory tympani,

transparent behind the tympanic membrane, showed a somewhat darkly red-colored aspect, as seen in seriously affected cases with otosclerosis and which is known as the Schwartze sign.

The hearing loss is mostly small and can be located in the middle ear, the inner ear, or both. For a long time osteogenesis imperfecta was considered to be a more serious form of otosclerosis. This concept has been proved to be incorrect.

Stapes surgery in osteogenesis imperfecta has been considered to be more risky than in otosclerosis. After the period when fenestration of the lateral semicircular canal was performed,[7-12] the first report of a successful stapedectomy in osteogenesis imperfecta was given by Sooy[12] in 1960. Since then, a series of reports on stapes surgery in osteogenesis imperfecta has been published. Most of these reports were case studies or small series.[13-17] Since the late 1970s, the first reports on 10 or more stapedectomies have been published.[18-23] In 1982, Shea and Postma[20] published the largest series, 62 operated ears in 43 patients. Their hearing results were presented for only 51 ears with at least a 1-year follow-up. This was followed by Pedersen[24] in 1985 with surgical reports of 43 ears in 32 patients. The series of 62 ears discussed in this article, all from patients in the Netherlands, is as large as the two preceding reports. The short-term and long-term results of investigations of this series will be presented in detail.

PATIENTS AND METHODS

This study of the results of surgery on the ears of patients with osteogenesis imperfecta is part of a much wider study of the nature of the hearing loss and the degree of progression of that loss. First, the results of stapes surgery in patients with osteogenesis imperfecta in the University Hospital Nijmegen Department of Otorhinolaryngology were collected and published.[23,25] To this study could subsequently be added patients, known to other ear, nose, and throat surgeons in the Netherlands, who had also undergone ear surgery.[26] An association of patients in the Netherlands with osteogenesis imperfecta (VOI) has also given its support in contacting new patients. These activities started in 1984 and have now resulted in a series of

62 ears in 49 patients who have undergone ear surgery for osteogenesis imperfecta. For all patients, no distinction is made between osteogenesis imperfecta congenita and osteogenesis imperfecta tarda or any other subclassification in the diagnosis.[1-3]

In 58 of these 62 ears, stapes surgery had been performed; in 2 of them, a fenestration of the semicircular canal had been performed, and in 2 of them, a replacement of the incus was performed. Almost all patients could be followed up and have been visited to obtain a highly detailed medical history. Pre- operative and postoperative audiograms and the surgical reports were gathered from the patient's medical files. Since many otologists have been involved over a long period of time, not all of the details we sought were available. Also, the methods of stapedectomy were different. Most patients could be traced personally and assisted in providing new audiometric data, thereby increasing the duration of their follow-up period.

We present data concerning the preoperative and postoperative hearing levels, the immediate postoperative hearing gain, the hearing gain at follow-up, and the increased postoperative sensorineural hearing loss. Long-term results in terms of average pure-tone hearing thresholds at 0.5, 1, and 2 kHz are also given and are related to the period of follow-up in months.

RESULTS

This study describes 31 women between the ages of 21 and 66 years (mean, 39.4 years) and 18 men between the ages of 16 and 62 years (mean, 38.0 years). Of these 49 patients, 10 had hearing loss unilaterally. Conductive or mixed hearing loss bilaterally was present in the remaining 39 patients. Eleven patients underwent stapedectomy bilaterally. Two of those 49 patients had a fenestration of the lateral semicircular canal and two others also had an incus interposition. Of those four patients, two have had a stapedectomy in the other ear, making a total of 58 stapedectomies, of which 17 were performed at the Department of Otorhinolaryngology, University of Nijmegen.

The mean age for the onset of hearing loss in 43 patients was 18.4 years. For 4 of 47 patients, the age at onset of the hearing loss remains unknown. In 27 women, the

onset of hearing loss occurred between 5 and 37 years of age (mean, 16.1 years of age); for 16 males, the onset of hearing loss occured between 7 and 46 years of age (mean, 21.8 years of age). The mean age at the time of the first stapedectomy was 30.6 years. Thirty-one women underwent surgery between 10 and 63 years of age (mean, 30.4 years of age), and 18 men underwent surgery between 16 and 50 years of age (mean, 31.6 years of age).

The hearing results of 44 of 58 stapedectomies are illustrated in Figures 1 through 3. For 2 operations (ears 43 and 44) the preoperative audiogram could no longer be found; nevertheless they are included in Figure 3.

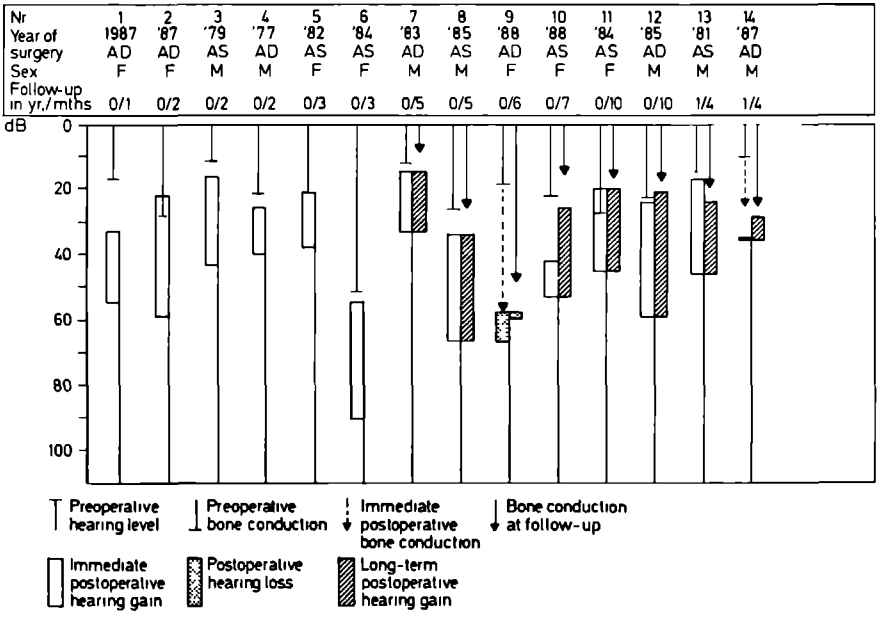

Figure 1: Results of stapedectomy in osteogenesis imperfecta for patients 1 through 14 in terms of the average pure-tone threshold (in decibel hearing level) for the frequencies 500, 1000, and 2000 Hz. AD indicates right ear; AS, left ear.

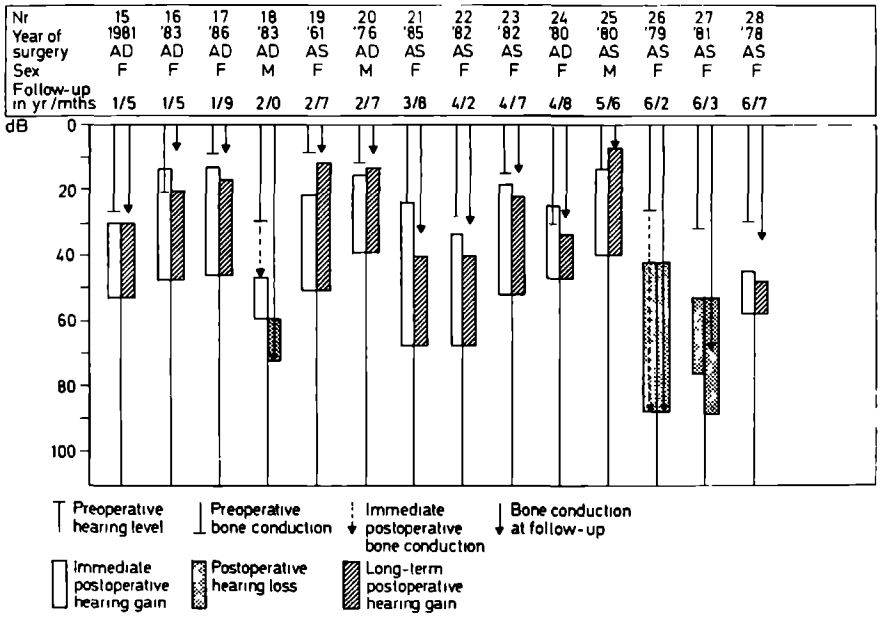

Figure 2: Results of stapedectomy in osteogenesis imperfecta for patients 15 through 28 in terms of the average pure-tone threshold (in decibel hearing level) for the frequencies 500, 1000, and 2000 Hz. AD indicates right ear; AS, left ear.

For 14 ears in 11 patients with osteogenesis imperfecta who underwent stapes surgery in the period from 1968 through 1986 at the Department of Otorhinolaryngology at our hospital, the preoperative and postoperative hearing levels have already been published.[25] The order of presentation of the results in that article corresponds with Nos. 45 to 58, inclusive of the operated ears in the present study. All of the other data concerning these ears are included in Tables 1 through 5.

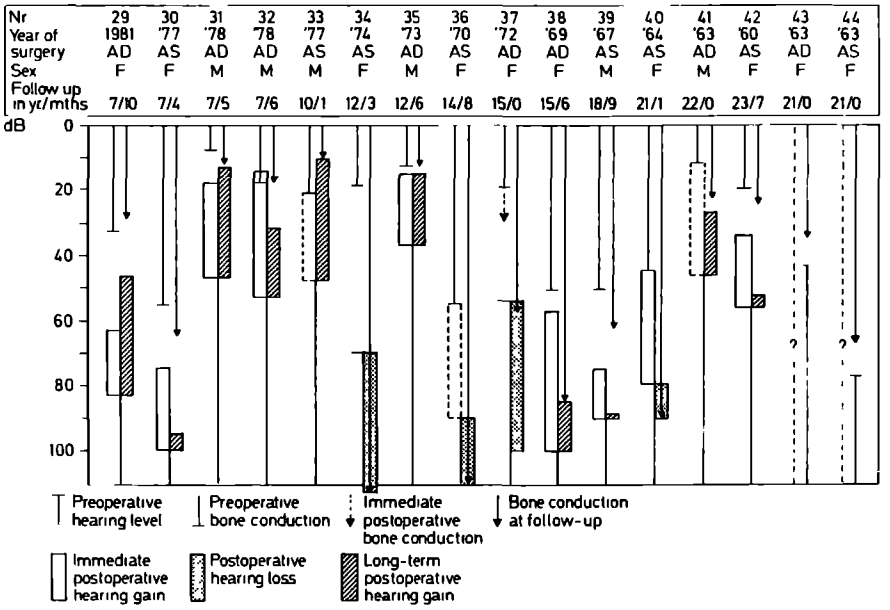

Figure 3: Results of stapedectomy in osteogenesis imperfecta for patients 29 through 44 in terms of the average pure-tone threshold (in decibel hearing level) for the frequencies 500, 1000, and 2000 Hz. AD indicates right ear; AS, left ear.

SHORT-TERM RESULTS (3 AND 12 MONTHS)

Hearing gain

In Table 1, our results are compared with those of the earlier American and Danish series.[20,24] Because of the compatibility with the Danish study, we decided to present the results in 58 easrs after 3 months. To be able to compare data with the American study, the results of stapes surgery after 12 months in 46 ears are also presented.

Table 1: Hearing results 3 and 12 months after stapes surgery

	No of Ears	Hearing gain > 10 dB		Without notable change < 10 dB		Worse	
		After 3 mo (%)	After 12 mo (%)	After 3 mo (%)	After 12 mo (%)	After 3 mo (%)	After 12 mo (%)
This study	58	49 (85)	...	5 (9)	..	4 (7)	...
	46	...	37 (81)	...	5 (11)	. .	4 (9)
Shea and Postma (1982)[20]	51	NA	43 (84)	NA	6 (12)	NA	2 (4)
Pedersen (1985)[24]	42	42 (100)*	NA	0 (0)	NA	0 (0)	NA

Note: NA indicates not applicable for lack of data
* Inclusive hearing improvement less than 10 dB.

Table 2: Air-bone gap 3 and 12 months after stapes surgery

	No of Ears	Air-bone gap < 10 dB		Air-bone gap 10 - 20 dB		Air-bone gap > 20 dB	
		After 3 mo (%)	After 12 mo (%)	After 3 mo (%)	After 12 mo (%)	After 3 mo (%)	After 12 mo (%)
This study	52	37 (71)	...	11 (21)	...	4 (8)	.
	40	...	31 (78)	...	5 (13)	...	4 (10)
Shea and Postma (1982)[20]	51	NA	38 (75)	NA	NA	NA	NA
Pedersen (1985)[24]	42	26 (62)	NA	9 (21)	NA	7 (17)	NA

Note: NA indicates not applicable for lack of data

Three months after the operation, 49 (85%) of 58 ears in which stapes surgery had been performed showed a hearing gain of more than 10 dB. In 5 ears (Nos. 14, 34, 36, 37, and 57)(9%) the preoperative hearing threshold was increased by less than 10 dB, or was unchanged. Furthermore, 3 of these ears (Nos. 34, 36, and 37) showed a considerable increase in hearing loss more than one year after the operation. In one ear (No. 57) deafness persisted unchanged. One ear (No. 14) showed a slight increase in the perceptive component, directly related to the operation.

The hearing in four ears (Nos. 9, 26, 27, and 44)(7%) deteriorated within the first post-operative year. Three of these (Nos. 9, 26, and 44) showed a considerable increase in perceptive hearing loss with an almost totally closed air-bone gap directly after the operation. In another ear (No. 27) there was an isolated increase in the air-bone gap with an unchanged perception threshold directly after the operation. Within one year, this patient had developed a perception loss with stabilization of the air-bone gap to the preoperative value of 20 dB.

After 12 months, 37 (81%) of 46 ears showed a hearing gain of more than 10 dB above the preoperative hearing threshold. In 5 ears (Nos. 14, 34, 36, 37, and 57)(11%), the postoperative gain was less than 10 dB, or there was no change. These 5 ears showed the same hearing characteristics after 3 months. The hearing in 4 ears (Nos. 18, 26, 27, and 44)(9%) had deteriorated. In 3 ears (Nos. 26, 27, and 44), there was no change in the situation after 3 months postoperatively. Ear 9 has not yet been studied for 12 months and is, therefore, not discussed here. Despite an initial hearing gain in ear 18, considerable increase in perception loss occurred within the first year postoperatively. In comparison with the preoperative condition, the hearing threshold is, therefore, reduced.

Air-bone gap

Table 2 compares the size of the air-bone gap in this study with the results from the American and Danish studies.

After 3 months, 37 (71%) of 52 ears in our series showed a completely, or almost completely, closed air-bone gap (less than 10-dB difference between bone and air conduction). In 11 (21%) of these 52 ears, there was a direct postoperative air-bone

gap of 10 to 20 dB. In 3 ears (Nos. 29, 30, and 39)(6%) this value was between 20 and 30 dB. There was a conductive loss of more than 30 dB in 1 (No. 27)(2%) of the 52 ears.

After 12 months, 31 (78%) of 40 ears showed a completely, or almost completely, closed air-bone gap following stapes surgery. In 5 (13%) of these 40 ears, an air-bone gap of 10 to 20 dB persisted, and in 4 ears (10%), the gap was 20 to 30 dB. There was some further improvement in the air-bone gap in our series between 3 and 12 months.

Incomplete data

Partly because of the extent of the hearing loss in six ears from four patients, it is no longer possible to establish if there was an air-bone gap after 3 and 12 months. These ears (Nos. 34, 36, 37, 43, 44, and 57) are, therefore, excluded from Table 2. It is known that two of these ears (Nos. 34 and 37) from the same patient showed no change in hearing during the first year postoperatively. Audiometric details for calculating air-bone gaps were unavailable. Another patient (ear 36) showed a subjective improvement in hearing postoperatively. However, the first postoperative measurement known to us took place after 5 years, which, after a steadily progressive hearing loss, established a completely deaf ear. One patient (ear 57) had become steadily deaf in both ears. Audiograms over a period of almost 30 years show considerable progression in her hearing loss. There was uncertainty with regard to the extent of the loss of perception. Nonetheless, the worst ear had undergone an operation in the hope that, after reduction of the conductive loss, some useful sensorineural remnants of hearing would become available. However, this stapedectomy was not followed by any improvement. From another patient who underwent stapedectomy bilaterally (ears 43 and 44), no preoperative or immediate postoperative audiograms are available. However, after 21 years the air-bone gap is closed bilaterally.

Hearing gain

Long-term results are available for 40 ears in which stapes replacement surgery was performed. The follow-up period varies from 2 to 24 years with an average of 9.6 years (Table 3). A hearing gain of more than 10 dB above the preoperative threshold was present in 27 (68%) of the 40 ears. The decline in hearing gain from 85% after 3 months to 68% in the long-term follow-up period is hardly the result of changes in the airbone gap. After 3 months, 71% of the ears showed a closed air-bone gap, falling to 70% over a longer period. A gradual increase in perception loss during the follow-up period, as shown in Figures 1 through 3, would appear to explain this loss in hearing gain.

Table 4 shows the average hearing gain for both the 3-month and the 12-month postoperative period and for the long-term follow-up. The results are compared with those from the Danish series. Despite incomplete data in the American series, extrapolation shows a global hearing gain in the period after 12 months.

Table 3: Hearing gain and air-bone gap after stapes surgery. Long-term results

	No. of Ears	Follow-up in years	Hearing gain	Air-bone gap		
			> 10 dB (%)	< 10 dB (%)	10-20 dB (%)	> 20 dB (%)
This study	40	2-24	27 (68)	...	...	...
	37	...	...	26 (70)	7 (19)	4 (11)
Shea and Postma (1982)[20]	24	2-18	18 (75)	NA	NA	NA
Pedersen (1985)[24]	22	2-17	17 (77)	5 (23)	NA	NA

Note: NA indicates not applicable for lack of data.

Table 4: Mean hearing gain at 3 and 12 months postoperatively and long-term

	No. of Ears	Postoperative, dB HL		
		3 Mo	12 Mo	Long-term
This study	56	24.0	...	...
	44		22.8	16.3
	38	...	...	...
Shea and Postma (1982)[20]	51	NA	23.5 ± 1.0*	NA
Pedersen (1985)[24]	42	25	NA	
	22		NA	17

Note: Mean value: 0.25, 0.5, 1, and 2 kHz; HL indicates hearing level.
NA indicates not applicable for lack of data.
* Extrapolation.

In the follow-up period, 5 (13%) out of 40 ears showed unchanged hearing or a hearing gain of less than 10 dB when compared with the preoperative hearing threshold. After an initial hearing gain that persisted for some years, 4 of these 5 ears (Nos. 30, 39, 42, and 46) developed long-term perception loss with an unchanged air-bone gap. The other ear (No. 57) with an unchanged hearing threshold remained deaf, whereby the perception threshold could not be measured, as had been the case preoperatively.

Air-bone gap

Long-term data regarding the air-bone gap are available for 37 of 40 ears. In the other 3 ears (Nos. 34, 36, and 55), the extent of the hearing loss makes it impossible to determine the perception threshold, and these ears are, therefore, excluded from Table 3.

Table 5: Mean air-bone gap preoperatively and postoperatively at 3 and 12 months and long-term

	No. of Ears	Preoperative	Postoperative, dB HL		
			3 Mo	12 Mo	Long-term
This study	38	34.6	9.6	7.7	11.7
Shea and Postma (1982)[20]	24	NA	NA	NA	NA
Pedersen (1985)[24]	22	25	NA	NA	15.7

Note: Mean value: 0.25, 0.5, 1, and 2 kHz; HL indicates hearing level.
NA indicates not applicable for lack of data.

Twenty-six (70%) of 37 ears have a completely, or almost completely, closed air-bone gap in the follow-up period. In 7 ears (19%), there is an air-bone gap of 10 to 20 dB. This figure is between 20 and 30 dB in 2 ears (Nos. 39 and 42)(5%). A conductive loss of more than 30 dB is present in 2 (Nos. 30 and 37)(5%) of 37 ears. It can be seen from Figures 1 through 3 and from Tables 2, 3, and 5 that the follow-up value of the air-bone gap shows little change from the direct postoperative phase.

Increase in sensorineural hearing loss

During the follow-up period, of 58 ears 11 (Nos. 9, 14, 18, 26, 27, 34, 36 through 38, 40, and 44) showed a perception loss of 10 dB or more when compared with the preoperative perception threshold. This increase in perception loss appears to be directly related to the operation in six ears (Nos. 9, 14, 18, 26, 27, and 37). In two (Nos. 9 and 37) of these six ears, a floating footplate occurred as a complication. In two ears (nos. 26 and 27) with a massive and bony footplate, a vestibulotomy had

been performed at the edge of the oval window. This has not been of help to us in the removal of the very thick footplate. Postoperatively, the hearing levels deteriorated. The other two ears (Nos. 14 and 18) showed no intraoperative complications.

In five ears (Nos. 34, 36, 38, 40, and 44), the progressive perception loss is not directly related to the operation, occurring more than one year thereafter, so that it is quite likely that an increase in the perception loss would have occurred whether or not an operation had been performed. In two ears (Nos. 18 and 37), there is a clear progression of the perception loss both in direct relation to the operation and during the follow-up period after one year.

The observation that a progressive perception loss can arise unrelated to stapes surgery is supported by the occurrence of such a loss of perception in both ears. From four of five cases mentioned above (Nos. 34, 36, 38, 40, and 44), the contralateral ear also shows such a loss of perception. The late deafness in the fifth ear (No. 40) is the result of direct external trauma. A slight increase in the perceptive threshold can be seen in six other ears (Nos. 21, 30, 39, 41, 48, and 52).

OTHER EAR OPERATIONS

As well as 58 stapedectomies, we also saw the results of two fenestrations and two incus replacement procedures in four patients. Two of these patients underwent a stapedectomy in the other ear (Nos. 21 and 40). The fenestration operations were performed in 1948 and 1953 and led to no subjective improvement or deterioration in the hearing threshold (Figure 4). Audiometric data could no longer be traced. The audiograms made during the last 20 years in these patients show a gradually progressive perceptive hearing loss of 20 dB with an unchanged air-bone gap averaging 40 dB.

Two patients with a large conductive hearing loss underwent incus replacement procedures. In one 16-year-old patient who, as a child, had twice undergone mastoidectomy, the incus was luxated and the stapes was intact and mobile. A chain reconstruction took place using an allograft incus. The air-bone gap was reduced from 40 to 20 dB. In a 36-year-old patient, an intact and mobile stapes was found as well as

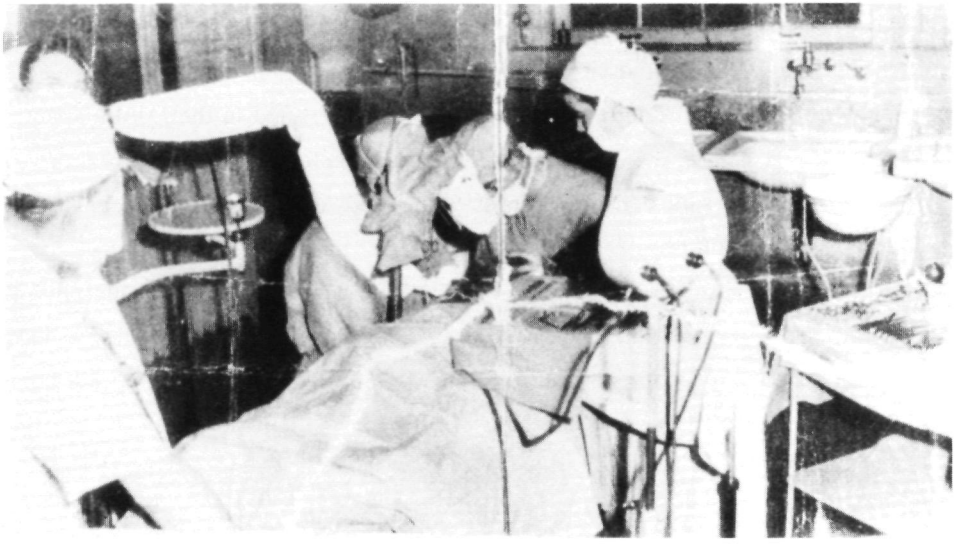

Figure 4: Fotograph of Dr. Gerlings performing a fenestration of the semicircular canal in a patient (No. 40) suffering from osteogenesis imperfecta. At that time (1948) it was a new topic in surgery for otosclerosis, which was the reason for publication in the Utrechtse Courant.

an incus with a thin and shortened process. A chain reconstruction took place using an autologous incus. The air-bone gap was reduced from 50 to 30 dB, but there was no improvement in hearing since there was a postoperative perception loss of 15 dB. Although patients with osteogenesis imperfecta have an increased risk of fracture of the base of the skull, there are no indications that this could have played a role in the conductive loss established in these two patients.

DISCUSSION

The results of stapes surgery in patients with osteogenesis imperfecta in the Netherlands are presented in such a way that they can be compared with the results

of two earlier American and Danish studies.[20,24] The present study does show an earlier onset of hearing loss. The average age at the onset of the hearing loss was 18.4 years, while in the Danish study it was 23 years. The age at which stapes surgery took place, however, is the same. In this series it was 30.6 years, and in the Danish study it was 31 years. The data in the American study are too sketchy to allow comparisons to be made. This study states that the onset of hearing loss is especially seen in the second decade (42% of cases).

The results of stapes surgery in osteogenesis imperfecta are compared in the present study with the American and Danish studies. Since each of these studies used a different post-operative investigation moment, 3 and 12 months, individual comparisons are more difficult (Table 1).

In our study, after 3 months 85% of the operations had led to a hearing gain of more than 10 dB. The Danish study by Pedersen[24] achieved a 100% success rate, although this included those patients with a hearing gain of less than 10 dB. The details of the hearing thresholds in the Danish study, which agreed with Figures 1 through 3 in our study, showed that four to six of these ears had a hearing gain of less than 10 dB. This reduces the 100% score in the Danish study to 86% or 91%. In the present study, there was a hearing gain of more than 10 dB in 81% of 46 operated ears after 12 months. The results in the American study are almost the same, 84% in 51 ears.

An inventory was also made of the presence and size of a direct postoperative air-bone gap (Table 2). In the present study, 37 (71%) of 52 ears had a closed air-bone gap after 3 months; in the Danish study, this was found in 26 (62%) of 42 ears. After 12 months, 31 (78%) of 40 ears in our study had a closed air-bone gap; in the American study, the results were 38 (75%) of 51 ears.

The results of stapes surgery after 3 and 12 months are more or less the same in the present, Danish, and American studies. Tables 4 and 5 present the average hearing gain and the air-bone gap, as far as these data were available, alongside each other. This shows that there is a long-term reduction of approximately 8 dB in hearing gain, just as found by Pedersen and Elbrønd,[21] and that the air-bone gap remains more or less the same.

Our series and the Danish series present the collected results of a large number of ear, nose, and throat surgeons, unlike the American series, which comes from one

center. In this respect, the results herein compare favorably with the other two studies. The number of operated ears with a follow-up of more than two years is almost the same in our study as in the American and Danish studies together. All three studies have patients with extremely long follow-up periods of 17, 18, and 24 years. A hearing gain of more than 10 dB above the preoperative hearing threshold in the follow-up period is present in 27 (68%) of 40 ears in the our study (Table 3). Shea and Postma[20] found a comparable hearing gain in 18 (75%) of 24 ears; Pedersen[24] found this in 17 (77%) out of 22 ears. The air-bone gap in the three studies after 3 and 12 months showed little difference, but long-term individual comparison of these data is not really possible. In our study, there was a completely, or almost completely closed air-bone gap in 26 (70%) of 37 ears; while this percentage was 71% and 78% after 3 and 12 months, respectively (Tables 2 and 3). Pedersen[24] reported this in his figures for 5 (23%) of 22 ears. Shea and Postma[20] did not report the air-bone gap in the follow-up period.

It is as important to analyze further the disappointing results of stapes surgery in osteogenesis imperfecta as it is to analyze short-term and long-term successes. Despite the fact that the data regarding these operations had to be collected from many different sources, it is clear in assessing the increase in the perception loss that two separate possibilities may be involved. The first possibility is that the hearing loss increases in direct relationship to the operation and that there is a causal connection. This is true for 6 (10%) of 58 ears in our series without this event having led to complete perception loss in those ears. Second, it is possible that the long-term increase in perceptive hearing loss results principally from the natural course of the disease,[24,27] especially since the same progression is often seen in the other, nonoperated on ear of the same patient. These disappointing long- term results need not necessarily be caused by the stapes surgery performed.

The results of the American series from one center[20] differ very little from the current study and the Danish study, each of which reviewed data gathered from many places in these countries. The rarity of this disease and the occasionally remarkeable surgical findings, together with the sometimes severe long-term and short-term progression of the perceptive hearing loss, support our contention that such surgery should take place in centers specialized in ear surgery.

Our conclusion is that the long-term and short-term results of stapes surgery in osteogenesis imperfecta are sufficiently encouraging to justify continuing with this form of treatment.

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CHAPTER 6

STAPES SURGERY IN OSTEOGENESIS IMPERFECTA. ANALYSIS OF POSTOPERATIVE HEARING LOSS.

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ABSTRACT

The disappointing results in 12 of 58 stapedectomies, including four revision operations, performed on osteogenesis imperfecta patients were analyzed and compared with reports in the literature.

It is concluded that the results described as disappointing were not always the product of the stapes operation. A progressive sensori-neural hearing loss arising independently of the operation as a result of progression in the disease process of osteogenesis imperfecta appears to have a severe influence on the final hearing threshold.

INTRODUCTION

Osteogenesis imperfecta is characterized by brittleness of the bones, blue sclerae, and progressive hearing loss. The hearing loss usually begins in the second or third decade. It can be a pure conductive or a mixed loss. Pure perception losses, especially of the higher frequencies, are common [1] The conductive component in the hearing loss is usually the result of fixation of the stapes footplate, as in otosclerosis, sometimes there is a stapes fracture. Until the 1970s, the middle ear changes in osteogenesis imperfecta were considered to be a severe form of otosclerosis [2 4] Stapes surgery in osteogenesis imperfecta was therefore considered to be risky [5] On histological, biochemical, and clinical genetic grounds, it must be recognized that otosclerosis and osteogenesis imperfecta are not only recognisably different disease entities,[6 16] but also that osteogenesis imperfecta represents a group of various different disease processes that sometimes have very similar clinical manifestations [17 20]

To improve the hearing loss, fenestration of the lateral semicircular canal was performed in the 1940s and 1950s,[2 21 25] followed later by stapes mobilisation [23 25 26]. These operations had little success. The first successful report of stapedectomy in osteogenesis imperfecta appeared in 1960 [23] More publications followed later, usually covering a small number of operations with variable success.[5 25 27 37] It was not until the 1980s that a few series were published that reported on ear operations in more

than 10 patients. The results were usually good.[38-42]

The operative findings and the short-term and long-term results of stapes surgery are reported, especially in the three largest studies.[39,40,42]

This article presents an analysis of the disappointing results among the 58 ears in the Dutch series of stapes operations for osteogenesis imperfecta. A review of the relevant literature is also given.

PATIENTS AND METHODS

We studied hearing loss in sufferers of osteogenesis imperfecta by collecting data on stapes surgery in this disease. We combined data from the Nijmegen series[37,41] with those from other Dutch otologic surgeons. Some of these cases were reported spontaneously by these otologic surgeons following an appeal for such cases, while others were traced through a study of hearing loss in Dutch patients with osteogenesis imperfecta. The Dutch Association of Patients with Osteogenesis Imperfecta also lent its active support. A retrospective study of the operation reports was therefore made, and where possible, all audiological data were traced. At the same time, an attempt was made to extend the follow-up period by performing new pure tone audiometry studies. Other, non-otological data such as the number of fractures were also collected.[42] This Dutch series contained 58 stapedectomies in 47 patients with osteogenesis imperfecta. They were operated on during the period from 1960 to 1988 for fixation of the stapes. In 4 of the 58 ears, a revision operation was also performed. In 12 of the 58 stapes operations, the ultimate results proved disappointing, either directly after the operation and within a period of 12 months, or after more than 12 months. These operations were in 10 patients - 3 men and 7 women ranging in age from 15 to 45 years - who underwent stapes surgery between 1963 and 1988.

In order to be considered as disappointing, a result had to meet the following criteria:

1. Directly after the operation: an increase in the hearing loss, failure to achieve a hearing gain of more than 10 dB Fletcher-index (mean hearing loss at 0.5, 1, and 2 kHz), or an increase of the bone conduction threshold of 10 dB Fletcher-index or more despite an improvement in the air conduction threshold

of more than 10 dB Fletcher-index.

2. After 12 months post-operatively: an increase in the air conduction threshold of more than 20 dB Fletcher-index, or an increase of the bone conduction threshold of an average of 15 dB or more Fletcher-index.

We looked for common factors in these disappointing results (presumed failures) as compared with the successful operations. Features such as age at onset of hearing loss, the age at which the first stapes operation took place, the number of fractures, the sex of the patient, the technique of stapes surgery, the perioperative findings, and the preoperative bone conduction thresholds, from our complete group of 58 ears and from comparable studies[5,25,29-35,38-40] were compared retrospectively in order to see if there are indicators of a reduced chance of a successful operation.

RESULTS

Data could be gathered from 47 patients who had undergone operations in the Netherlands for stapes fixation during the period from 1960 to 1988. There were 17 men and 30 women; the sex ratio was therefore 1 to 1.8.

Table 1: Sex distributions of patients

	Shea & Postma[39]	Pedersen & Elbrønd[40]	Others[5,25,29-35,38]	This series[41,42]	Total	Presumed failures
	No.of Pts	No.of Pts	No.of Pts	No.of Pts	No.of Pts	No.of Pts
Men	14	13	11	17	55	3
Women	29	19	41	30	119	7
Unknown	-	-	4	-	4	-
M:F -ratio	1 : 2.1	1 : 1.5	1 : 3.7	1: 1.8	1 : 2.2	1 : 2.3

Table 1 also presents the sex ratio for the patient groups of an American study,[39] a Danish study,[40] and a combination of 10 studies compiled by us.[5,25,29-35,38] The data from the 12 of 58 ears in which the results could be described as disappointing are listed separately (presumed failures).

Of 174 out of 178 patients who underwent ear operations, there are 119 women (68%) and 55 men (32%). Table 2 notes the number of fractures for our patients as well as for those of other series. The age (by decade) at which the first stapes operation was performed is stated for each patient in Table 3. The ages in the Dutch series range from 10 to 63 years, with an average of 30.6 years. For the 12 ears in which results were considered disappointing, the age at operation was even lower. For the 6 of these 12 ears in which there was an increase in hearing loss directly after the operation, the average age at stapes surgery was 20.0 years, as opposed to 36.3 years for the 6 ears with hearing loss that occured later.

Table 2: Number of fractures

	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Presumed failures	
No.of fractures	No. of Pts	%	No. of Pts	%	No. of Pts	%	No. of Pts	%	No. of Pts	%
< 3	17	40	-	-	4	7	5	11	2	20
3 or more	26	60	-	-	14	25	40	85	7	70
Unknown	0	0	-	-	38	68	2	4	1	10
0	-	-	0	0	-	-	1	2	0	0
1 - 5	-	-	6	19	-	-	14	30	3	30
6 - 9	-	-	5	17	-	-	3	6	0	0
10 - 29	-	-	15	47	-	-	19	40	5	50
30 or more	-	-	4	13	-	-	8	17	1	10
Unknown	-	-	2	6	-	-	2	4	1	10
Total	43		32		56		47		10/47	

Note: Dash - indicates not applicable for lack of data.

Table 3: Age at time of first stapes operation

	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Total		Presumed failures	
Age (yrs)	No. of Pts	%	No. of Pts	%	No. of Pts*	%	No. of Pts	%	No. of Pts	%	No. of Pts	%
0 - 9	-	-	0	0	1	3	0	0	1	1	0	0
10 - 19	-	-	4	13	6	21	7	15	17	16	2	20
20 - 29	-	-	14	44	7	24	18	38	39	36	4	40
30 - 39	-		7	22	4	14	11	23	22	20	3	30
40 - 49			4	13	9	31	8	17	21	19	1	10
50 - 59			3	9	1	3	2	4	6	6	0	0
60 or more	-	-	0	0	1	3	1	2	2	2	0	0
Total	-		32		29		47		108		10/47	
Mean age	-		31.0		32.3		30.6		31.2		27 6	
Range (yrs)	-		-		9 - 66		10 - 63		9 - 66		15 - 44	

Note: Dash - indicates not applicable for lack of data.
* Data unknown for 27 patients.

Table 4: Age at onset of hearing loss

	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Total		Presumed failures	
Age (yrs)	No. of Pts	%	No. of Pts	%	No. of Pts	%	No of Pts	%	No of Pts	%	No of Pts	%
0 - 9	2	5	2	6	1	2	10	21	15	9	3	30
10 - 19	18	44	11	34	4	7	16	34	49	28	5	50
20 - 29	8	20	11	34	6	11	11	23	36	20	1	10
30 - 39	5	12	6	19	2	4	4	9	17	10	1	10
40 - 49	5	12	2	6	0	0	2	4	9	5	0	0
50 or more	3	7	0	0	0	0	0	0	3	2	0	0
Unknown	0	0	0	0	43	77	4	9	47	27	0	0
Total	41		32		56		47		176		10/47	

Table 4 and Table 5 show that 26 of the 43 patients (60%) already had hearing loss before 20 years of age and that the average age at onset was 18.4 years. In the group with disappointing results, this was the case in 8 of 10 patients (80%), with an average age at onset of hearing loss of 16.6 years. On average, the age at onset of hearing loss in the Danish, American, and combined groups ("Others") was several years later.

Table 5: Mean age at onset of hearing loss

	Shea & Postma[39]	Pedersen & Elbrønd[40]	Others[5,25,29-35,38]	This series[41,42]	Total	Presumed failures
No of patients	-	32	37	43	112	10/47
Unknown	-	0	19	4	23	0
Mean age at onset	-	23 0	22 4	18 4	21 0	16 6
Range	-	-	9-36	5-46	5-46	8-32

Dash - not applicable for lack of data.

Table 6: Methods of stapes surgery

Methods of surgery	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Presumed failures	
	No. of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%
Fat/vein/Gelfoam-wire	-		22	51	25	35	6	10	2	17
Teflon-piston	-	-	7	16	1	1	20	35	6	50
Teflon-wire	-	-	0	0	6	8	20	35	3	25
Teflon-cup/loop	-	-	0	0	0	0	6	10	0	0
Vein-polyethylene strut	-	-	11	26	1	1	4	7	1	8
Malleus-handle piston	-	-	0	0	0	0	1	2	0	0
Autologue interposition										
Stapedioplasty	-	-	1	2	0	0	0	0	0	0
Portmann type II	-	-	0	0	0	0	1	2	0	0
Unknown	62	100	2	5	38	54	0	0	0	0
Total	62		43		71		58		12/58	

Dash - not applicable for lack of data.

Table 7: Types of stapes surgery

Types of surgery	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Presumed failures	
	No. of Ears	%	No. of Ears	%	No. of Ears	%	No. of Ears	%	No. of Ears	%
Total stapedectomy	62	100	37	86	39	55	31	53	10	83
Partial platinectomy	0	0	1	2	1	1	12	21	0	0
Stapedotomy	0	0	2	5	0	0	14	24	2	17
Partial stapedectomy	0	0	1	2	1	1	1	2	0	0
Unknown	0	0	2	5	30	42	0	0	0	0
Total	62		43		71		58		12/58	

Dash - not applicable for lack of data.

The various techniques for performing stapes surgery, as well as those for total stapedectomy, partial platinectomy, stapedotomy, and partial stapedectomy are listed in Table 6 and Table 7. In 31 of 58 ears (53%) a total stapedectomy was performed, but after 1980, partial platinectomy and stapedotomy were more frequently performed. Before 1980, only 4 of 27 ears (15%) were treated by partial platinectomy or stapedotomy; after 1980, 22 of 31 ears were (78%).

The operative findings in the stapes footplate, the stapes crura, and the middle ear mucosa in the region of the oval window are listed in Table 8. A moderate-to-severe thickening of the footplate was found in 32 of 58 ears (55%). In all the studies together, this was found in 134 out of 234 ears (57%). In the group with disappointing results, the footplate was thickened in 10 of the 12 ears (83%). Further differentiationshowed that the majority of the thickened footplates was solidly thickened - a finding sometimes observed in the form of an obliteration of the oval window. In the present study, this finding was seen in 22 of the 32 thickened footplates (69%). In the group with disappointing results and in the study of Shea and Postma,[39] all thickening of the footplate was solid. In 15 of 58 ears (26%) in the present study a soft or friable footplate consistency was reported, and in all the studies together, this was found in 61 out of 234 ears (26%). The group with

Table 8: Findings during stapes operation

Findings at operation	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29 35,38]		This series[41,42]		Presumed failures	
	No of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%
Footplate										
Fixed	62	100	43	100	70	99	54	93	11	92
Thick	31	50	23	53	48	68	32	55	10	83
Slightly	0	0	0	0	0	0	0	0	0	0
Moderately	0	0	0	0	0	0	10	17	0	0
Solid	31	50	0	0	0	0	22	38	10	83
Soft	4	6	6	14	36	51	15	26	2	17
Bleeding	0	0	0	0	1	1	8	14	3	25
Thick rims	14	23	0	0	0	0	11	19	4	33
Unknown	0	0	0	0	1	1	4	7	1	8
Stapes crura										
Fractured	0	0	5	12	14	20	10	17	0	0
Thin/atrophic	13	21	14	33	18	25	22	38	5	42
Brittle	0	0	11	26	0	0	0	0	0	0
Normal	49	79	12	28	32	45	19	33	4	33
Unknown	0	0	6	14	9	13	11	19	3	25
Mucosa										
Thick	0	0	12	28	3	4	7	12	5	42
Bleeding	18	29	13	30	6	8	12	21	5	42
Normal	44	71	21	49	8	11	24	41	3	25
Unknown	0	0	5	12	54	76	19	33	3	25
Total ears	62		43		71		58		12/58	

disappointing results shows no differences here. Thickened edges and/or bony apposition anteriorly and posteriorly on the footplate, which hinders a good approach, were seen in 11 of the 58 ears (19%). In all studies together this was seen in 25 out of 234 ears (11%). In the group with disappointing results, it was found in 4 of 12 ears (33%). A remarkable number of reports in the present study state that even the footplate itself bled easily during the operation (8 of 58 ears or 14%). In all studies together this was reported in 9 of 234 ears (4%), and in the group with disappointing results, in 3 of 12 ears (25%). The presence of a floating footplate is sometimes correlated to a thick and soft footplate. If it should be necessary to remove the stapes superstructure early, without being able to introduce a safety hole into the footplate, the chance of a floating footplate will clearly be increased, partly because of the

reduced fixation. This occurence was seen in 2 of the 12 ears (17%) with disappointing results. In all studies together, a floating footplate occurred in 5 of 234 ears (2%), with a resultant increase in sensorineural hearing loss.[30,32,42]

In 11 of 58 ears (19%), detailed information about the configuration of the stapes crura was not available. Normal crura were found in 112 out of 234 ears (48%), although there was some variation among the individual studies. In 10 of 58 ears (17%) the crura appeared to be interrupted. This finding was reported in 29 of the 234 ears (12%), with an individual variation of 0% to 20%. The crura were thin and/or atrophic in 22 of the 58 ears (38%). A total of 67 of the 234 ears (29%) had similar crura. In the group with disappointing results, thin and/or atrophic crura were found in 5 of 12 ears (42%), and there were no fractures.

A thickened mucosa was seen in 7 of the 58 ears (12%) and in 22 of the 234 ears (9%), with individual variations of between 0% and 28%. In the group with disappointing results, however, a thickened mucosa was found in 5 of the 12 ears (42%). It is also remarkable that in 12 of the 58 ears (21%) it was stressed that the mucosa bled readily, while in 19 ears (33%), there is no report of this; and the mucosa was described as normal in 24 of the 58 ears (41%). In all studies together, a remarkably haemorrhagic mucosa was reported in 49 of the 234 ears (21%). This abnormality, too, occurs more frequently in the group with disappointing results (5 of 12 ears or 42%).

In total, we established that for 12 of these 58 stapes operations (21%), the results directly after the operation or after a period of more than 12 months were disappointing according to our standards. The preoperative and postoperative hearing levels of these 12 ears in 10 patients are presented in Figs 1 through 7, together with the simultaneously recorded hearing levels in the 8 contralateral ears.

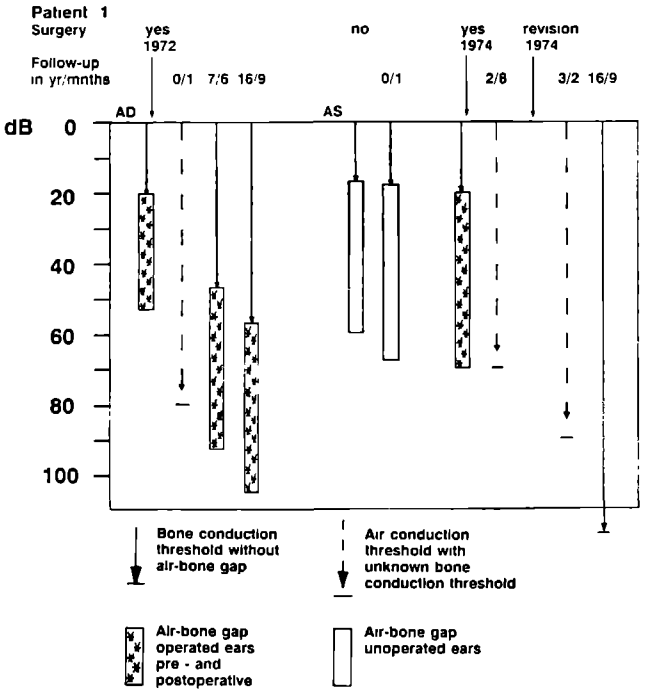

Figure 1: (Patient 1) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

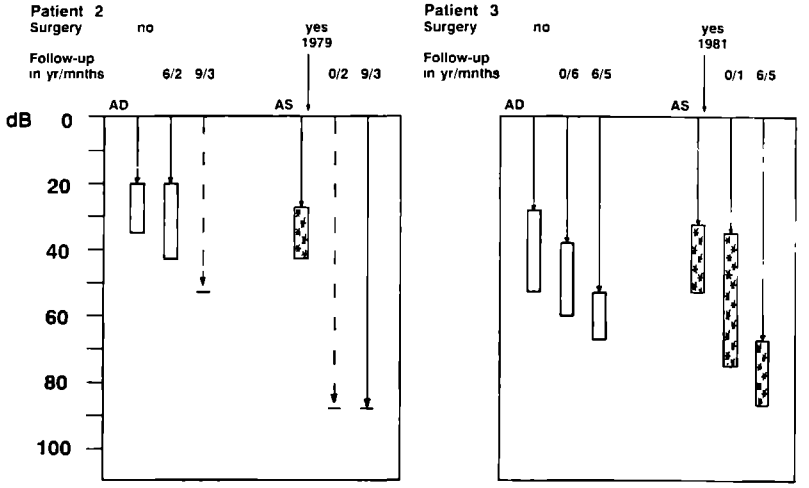

Figure 2: (Patients 2 and 3) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

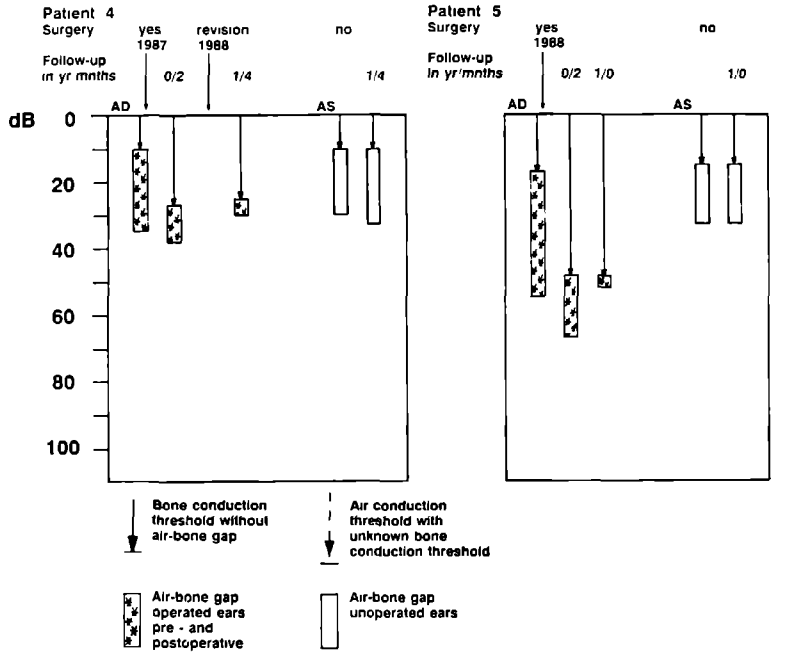

Figure 3: (Patients 4 and 5) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

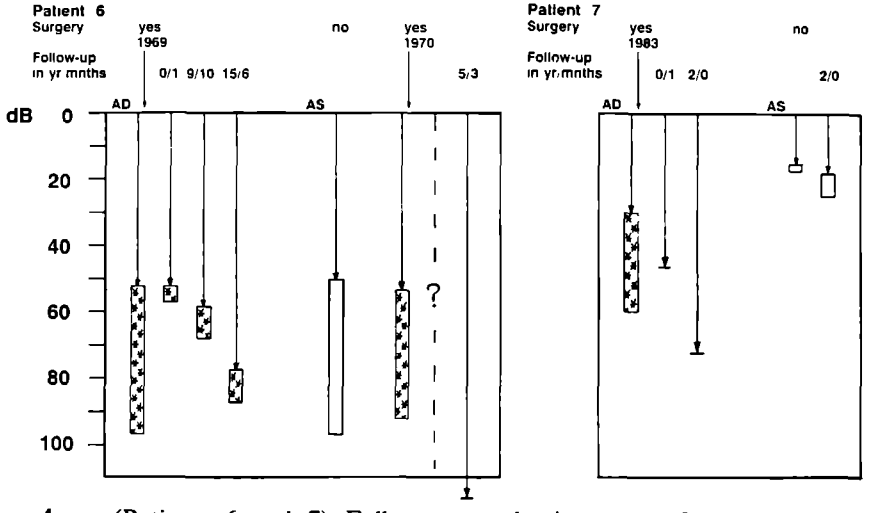

Figure 4: (Patients 6 and 7) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

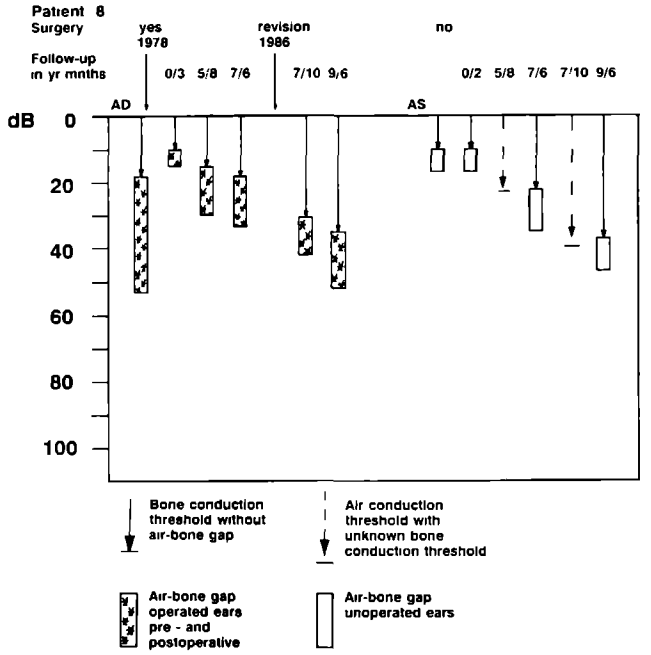

Figure 5: (Patient 8) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

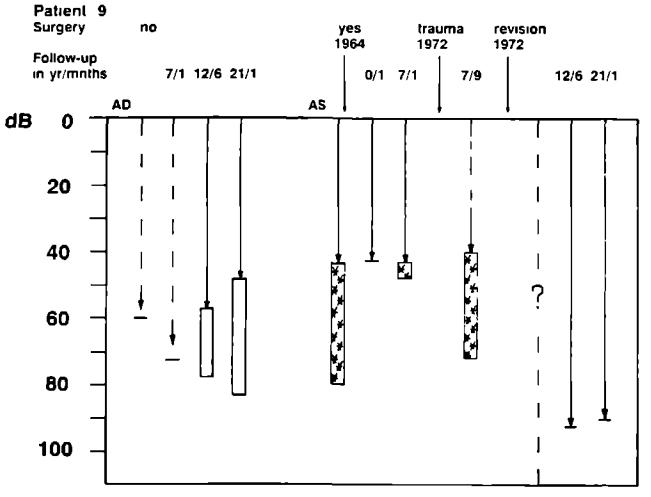

Figure 6: (Patient 9) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

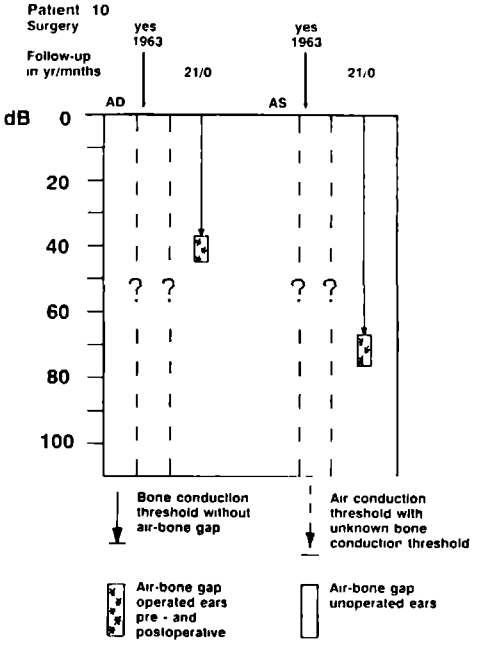

Figure 7: (Patient 10) Follow-up results in terms of average pure tone thresholds (decibels hearing level) for frequencies 0.5, 1, and 2 KHz.

Table 9 reports the ear, sex and age of each of these 12 patients, as well as the findings during operation, the type of piston used, the complications noted during operation as documented in the surgical report, and some other special findings. An increase in hearing loss compared with the preoperative hearing threshold was noted directly after the operation in 5 of the 12 ears (42%) (Figs 1 through 3; patients 1 right, 2, 3, 4, and 5). The hearing threshold was unchanged directly after the operation in 1 of the 12 ears (8%) (Fig 1; patient 1 left). An acceptable-to-good hearing gain was achieved in 5 of the 12 ears (42%) (Figs 4 through 6; patients 6 both, 7, 8, and 9). One of the 12 ears (8%) has been included in the totals although data are not available that could demonstrate any relationship between the operation and the hearing result (Fig 7; patient 10). It is remarkable that despite the findings and the

Table 9a: Findings at 12 stapedectomies in 10 patients with disappointing results. Immediate hearing loss.

Pt	Sex	Ear	Date	Age (y)	Method	Findings			Complications	Remarks	Bone/Air Conduction Hearing Levels (dB HL)		
						Footplate	Stapes	Mucosa			Preop	Postop	Follow-up
1	F	R	1972	15	Teflon	Very thick	Normal	Bleeding	Floating footplate	Immediate hearing loss	20/53	?/80	57/105
		L	1974	17	Teflon	Solid bony apposition	?	Thick	None	Adhesions; granulations; revision	20/70	?/70	ND/115
2	F	L	1979	25	Teflon	Solid bony; bleeding	Normal	Normal	Perilymph leakage	Immediate hearing loss	27/43	?/88	ND/88
3	F	L	1981	16	Teflon	Enormous, thick apposition	Thin; atrophic	?	Perilymph leakage	Immediate hearing loss	32/53	37/75	67/87
4	M	R	1987	20	Teflon-wire	Very thick	Normal	Normal	None	Immediate hearing loss; revision	10/35	27/38	25/30
5	F	R	1988	27	Teflon-wire	Very thick walls; soft; bleeding	Normal	Normal	Floating footplate	Immediate hearing loss	17/55	48/65	48/52

Note: HL = Hearing level; ? = unknown, ND = not detectable

Table 9b: Findings at 12 stapedectomies in 10 patients with disappointing results. Hearing loss at follow-up

Pt	Sex	Ear	Date	Age (y)	Method	Findings			Complications	Remarks	Bone/Air Conduction Hearing Levels (dB HL)		
						Footplate	Stapes	Mucosa			Preop	Postop	Follow-up
6	F	R	1969	44	Gelfoam -wire	Thick bony apposition	Thin; atrophic	Thick; bleeding	None	Small oval window niche	52/97	52/57	ND/87
		L	1970	45	Gelfoam -wire	Soft;thick bony apposition	Thin; atrophic	Thick; bleeding	None	Small oval window niche	53/92	(?Hearing gain)	ND/110
7	M	R	1983	37	Teflon -wire	Normal	Thin; atrophic	Hypertrophic; bleeding	None	Annoying bleeding	30/60	47/47	73/73
8	M	R	1978	22	Teflon	Thick fibrotic; bleeding	Thin atrophic	Thick bleeding	Posterior part footplate in vestibulum	Revision after 6 years	18/53	10/15	35/52
9	F	L	1964	36	Teflon	Bony; very thick	?	?	None	Trauma after 8 years; revision	43/80	43/43	ND/90
10	F	L	1963	34	Vein-strut	?	?	?	?	Not successful	?	?	67/77

Note: HL = Hearing level; ? = unknown, ND = not detectable

Table 10: Findings at five stapedectomies resulting in total deafness.

Pt	Sex	Study	Age (y)	Method	Findings			Complications	Remarks
					Footplate	Stapes	Mucosa		
11	?	Shea & Postma[39]	?	Piston,? type	Solid obliteration	?	?	?	Hearing loss within 1 year after revision
12	?	Shea & Postma[39]	?	Piston,? type	Solid bony apposition	?	?	None	Hearing loss 3 years after revision
13	F	Patterson & Stone[29]	25	Gelfoam -wire	Moderately thickened	Thin; atrophic	?	None	Immediate hearing loss
14	F	Kosoy & Maddox[30]	42	Gelatin-wire	Deep-set;soft mass on anterior edge	?	Normal	Premature stapes mobilization	Immediate hearing loss
15	M	Brosnan et al[32]	47	Piston,? type	Discrete margin, slight fixation	Normal	Vascular	None	Immediate hearing loss presumably due to surgical trauma

events (Table 9), no single ear became completely deaf after operation, although 3 of the 12 ears (patients 1 left and 6 both) developed a hearing loss of more than 90 dB at a later stage. In the other studies[5,25,29-35,38-40] complete deafness arose in 5 of 176 ears (3%) (Table 10[29,30,32,39]; patients 11 through 15). In 1 of the 5 ears (patient 12) the deafness arose only after three years, as apposed to the other 4 ears, in which a direct relationship with the operation could be established. In order to investigate if the size of the sensorineural component of the preoperative hearing loss could influence the chances of an unfavourable postoperative result, we collated the preoperative bone conduction thresholds and their averages from the various studies (Table 11). It is remarkable that in the present study, in the group with disappointing results, and in the study of Shea and Postma[39] the several sensorineural hearing thresholds are equally divided. In the study of Pedersen and Elbrønd[40] and the combined studies[5,25,29-35,38] it is principally the lowest perception thresholds that are present in the largest percentage. The averages of the preoperative bone conduction

Table 11: Mean preoperative bone conduction thresholds

Preoperative bone conduction	Shea & Postma[39]		Pedersen & Elbrønd[40]		Others[5,25,29-35,38]		This series[41,42]		Presumed failures	
	No of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%	No of Ears	%
0-20 dB	28	45	30	70	15	21	26	45	5	42
20-40 dB	14	23	9	21	3	4	22	38	3	25
40-60 dB	16	26	3	7	0	0	6	10	3	25
60-80 dB	3	5	0	0	0	0	1	2	0	0
80 dB or more	1	2	0	0	0	0	1	2	0	0
Unknown	0	0	1	2	53	75	2	3	1	8
Mean preoperative sensorineural hearing level			18 8*		12 2		26 1		29 3	
No of Ears			42		18		56		11/56	

Dash - not applicable for lack of data.
*Extrapolation from figures.

thresholds are clearly higher in the present study than in the other studies.

In the present study revision operations were performed in a total of 4 out of 58 ears (7%). In two, the long process of the incus proved to be eroded, in one case there were also remnants of a chronic otitis media, and in one, the revision was performed following considerable external trauma. Only in one case did the revision result in a slight improvement in hearing (Fig 3; patient 4). In the other three, a hearing loss resulted, most probably completely sensorineural in nature (Figs 1, 5, and 6; patient 1 left, 8, and 9).

In the other studies, revision took place in 15 of 176 ears (9%). The findings in 5 of these 15 revisions are known (Table 12[25,29,34]; patients 16 through 19). From the total of 9 revisions described, adhesions and granuloma formation were present in 3 of them. In one ear, the oval window was obliterated. In 3 ears, the incus was eroded and in one case the strut was too short - a finding that could also indicate erosion. In

Table 12: Findings at operation in 5 of 15 revisions

Pt	Study	Findings at revision	Hearing result
16	Opheim[25]	Polyethylene strut too short, replaced by longer one; floating footplate; fat mass under longer strut	Considerable improvement
17	Patterson and Stone[29]	Incus marked with multiple granulomata; granulomatous mass extended from under incus to fill oval window niche	Dead ear
18	Patterson and Stone[29]	Oval window closed with iceberg-type bone	18 dB hearing level
19	Cohen[34]	First revision: Teflon cup piston not found, no fistula; distal part of incus disappeared; TORP between incus and oval window membrane	50 dB air-bone gap
		Second revision: granuloma between shaft of TORP and rim of oval window, TORP trimmed	20 dB air-bone gap

one case trauma had loosened the piston.

Of the 19 revisions from all the studies, only 6 (32%) showed an adequate-to-good result or closure of the air-bone gap. In 5 ears there was deterioration of hearing and in one case it was unchanged. The data for 3 ears are unavailable. In 4 ears, deafness resulted that was as good as total.

DISCUSSION

It is probable that the clinical presentation and also the nature of the hearing loss in osteogenesis imperfecta are the same as in otosclerosis. The distribution with regard to sex shows a female predominance of at least 2 to 1 in the 174 operated cases of osteogenesis imperfecta. The figures known from operated cases of otosclerosis patients are almost exactly the same.[8,43,44] The onset of hearing loss before the 20th year was established in a total of 64 of 129 patients (50%) (Table 4), without a

descriptive definition of this level of hearing loss being given. Otosclerosis also presents at a very young age, but less frequently so than osteogenesis imperfecta. Robinson[45] found an onset of hearing loss before the age of 18 years in 610 of 4014 otosclerosis patients (15%). In our group with disappointing results, 8 of the 10 patients (80%) were hard of hearing before 20 years of age. The question arises as to whether patients with an increased risk can be recognized in advance. First of all, it appears that these patients already have considerable loss of hearing at an early age (Tables 4 and 5), and, generally, they come to operation at a younger age (4.5 years younger) than average (Table 3). In the group with an increase in hearing loss directly after the operation, the average age at stapes surgery is even as low as 20.0 years, as opposed to 36.3 years in the group with hearing loss in the long term. Furthermore, the at-risk patient has a solidly thickened footplate (83%) with thickened edges (33%) and haemorrhage (25%) (Table 8). The crura are thin and atrophic (42%). The mucosa of the middle ear is thicker than normal (42%) and also leads to troublesome haemorrhage (42%). It also appears that the at-risk patient has a higher preoperative bone conduction threshold (Table 11). On the other hand, the at-risk patient shows no differences with regard to sex (Table 1), the number of fractures (Table 2), or the materials used during stapes operation (Table 6). However, a total stapedectomy had usually been performed in the group with disappointing results (Table 7).

The findings and events during operation could be reasons for the ultimately poor result. In the group with an increase in the hearing loss directly after the operation, a solidly thickened footplate, large bony appositions, and an oval window that was difficult to access had a detrimental influence on the operative results in five of six ears. In the group with an increase in the sensorineural component of the hearing loss 12 months after the operation or later, no causal relationship with the disease or with the middle ear could be established in three of six ears. In the three other ears from this group in which a severe sensorineural hearing loss arose later on, the disease process itself proved to be the cause.

When there is a continuous progression of the sensorineural hearing loss as a result of the bone disease itself, there is a good chance that this will be bilateral. In nearly every nonoperated contralateral ear, an increase in the sensorineural component of the hearing loss could be established if the follow-up period was long enough. In the

group of 6 ears with an increase in hearing loss directly after the operation, a progression of the sensorineural hearing loss still occured in the follow-up period after the surgical accident.

Considering these data it can be concluded that stapes surgery in osteogenesis imperfecta has more pitfalls than in otosclerosis. The disease process itself leads to changes in the form and structure of the footplate, the stapes superstructure, and the other components of the ossicular chain, so that no two ears show exactly the same picture. That is why more complications are encountered than in the otosclerosis operation. It is remarkable that despite the increased number of complications, there were no deaf ears directly after the operation in this Dutch series of 58 ears, as opposed to other studies[29,30,32,39]. Revision operations proved to be risky, since in only 6 of 19 ears (32%) was a good result achieved.

A notable finding in this study was that a progressive sensorineural hearing loss that is not related to the operation can have an important if not decisive effect on the ultimate result. Not infrequently, an apparently good operative result can be destroyed in the short, but usually longer, term by a severe sensorineural hearing loss. It is unjustified to consider these operations as failures. Frequent postoperative measurement of the bone and air conduction thresholds, even after a good result, is necessary to answer possible questions about hearing loss of later onset. A reliable prediction of the ultimate hearing threshold in the long term is difficult to make because of the progressive inner ear deafness that is associated with the disease process. It is remarkable that the group with disappointing results directly after the operation was relatively young and had a high preoperative bone conduction threshold. All these patients proved to have complication-sensitive changes in the footplate and oval window. It is precisely this risk group that needs the highest care that we can offer, and such patients should only be treated by the most experienced of otologists.

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CHAPTER 7

SUMMARY AND CONCLUSIONS

One of the original aims of this study was to gain more insight into the progression and nature of the hearing loss in patients with osteogenesis imperfecta. During the course of the study, this aspect had to be limited to osteogenesis imperfecta type I. Sufficient data could be collected on osteogenesis imperfecta type I in fully investigated families to discover and describe the negative influence of selection of the study data.

Nevertheless during the study period, the availability of sufficient unpublished data on other non-lethal forms of osteogenesis imperfecta enabled us to conclude that hearing loss is also associated with type III and type IV. It is also possible that the frequency of hearing loss in type III is higher and even more severe than that found in type I. We therefore propose that this research be continued to investigate other types of osteogenesis imperfecta.

CLINICAL GENETIC RESEARCH

The segregation of the symptoms and the penetrance of the characteristics were analysed in 30 fully investigated family pedigrees with 144 random members. The calculated segregation analysis, or the ratio between the actual number of patients and the number of patients calculated on the basis of an autosomal dominant mode of inheritance was 70:72, i.e. 97%, which closely approaches the ideal score of 100% for an autosomal dominant syndrome.

The incidence of the separate characteristics, such as blue sclerae and bone fractures, were no different from those reported in the literature, namely 100% for blue sclerae and 87% for fractures. The average incidence of hearing loss was 43% and the percentages grew larger with increasing age and appeared to be age-related. It is striking that the average percentage of sufferers with hearing loss in various family studies is in agreement with the percentage found in our 144 subjects. We therefore consider the data from these studies to be correct and we assume that the other non-family studies and the study described in Chapter 3, were hindered by negative

selection. On the basis of these studies, we can conclude that the incidence of hearing loss in osteogenesis imperfecta type I is 43%. In addition, calculation of the penetrance in successive generations showed that there is a clear relationship between age and the progression of the hearing loss, which is illustrated in a plot diagram (Chapter 2; Figure 2). There were very few elderly patients with normal hearing. Dividing the family members into two groups with or without male-to-male inheritance did not produce any evidence of a genetically distinguishable type with an X dominant mode of inheritance, such as in the Alport syndrome.

HEARING LOSS AND AGE

The audiometric data from 142 sufferers were further analysed and for the sake of recognizing any selection bias, they were compared to those from a random sample of the same population. The extremely high incidence of hearing loss of 78% in the 142 sufferers is the result of considerable selection on an age of younger than 30 years. An analysis of the difference between the two groups showed that the patients were between 10 and 30 years of age with an average hearing loss of 30-50 dB, which exceeds the lower limit for social hearing.

The following conclusions could be drawn from the data after they had been corrected for the above-mentioned negative selection: the average hearing loss increased between the 10th and 45th year by 1 dB per year for the frequencies 0.5 to 2 kHz, by 1.1 dB per year for 4 kHz and by 1.7 dB per year for 8 kHz. The conductive component for all the frequencies remained constant at 0.4 dB over the total period. For patients in the post-operative phase after stapes surgery, a decrease in the hearing level of about 0.8 dB per year can be expected (Chapter 5). This hearing loss was almost completely perceptive, also on account of the difference between the bone and air conduction thresholds in the follow-up period.

Our present data show progression of the hearing loss (both conductive and perceptive) with increasing age and for the first time it has become possible to further describe this progression between the age of 10 and 45 years. The data also show a clear distribution of the severity of the hearing loss, even in the same age groups. The

conductive loss does not always deteriorate to such an extent that it forms a general indication for stapes surgery. Nevertheless the risk that a person suffering from osteogenesis imperfecta type I will be confronted by considerable hearing loss during adult life as a result of the disease, is in our opinion fairly high. Consequently, the onset of hearing loss besides other hindering factors which might result from the syndrome, such as bone fractures, is a factor for the patient to keep in mind when choosing an occupation. This auditory handicap will become most troublesome in the communicatively-geared occupations where people have to understand speech while there is a great deal of background noise. If the patient is suffering from considerable inner ear hearing loss, rehabilitation with a hearing aid will not be adequate for hearing speech under difficult (noisy) circumstances. Long-term avoidance of these more difficult hearing conditions, particularly noisy circumstances, will not always be possible at a more advanced age in every profession. The possibility of retraining also has its limitations. In our opinion therefore, it would be correct to take our present, although limited knowledge of the risk of progressive hearing loss in persons suffering from osteogenesis imperfecta type I into consideration when choosing a career or occupational training.

STAPES SURGERY

Although it was not explicitly mentioned that the patients described in Chapters 4, 5 and 6 and in the two large series in the literature were suffering from osteogenesis imperfecta type I, it is probably true of the majority of them, if not all. In isolated cases of osteogenesis imperfecta with hearing loss at a young age and serious symptoms resulting from many factors, it is very easy to be hesitant, especially in retrospective studies. It is for this reason that the authors preferred not to speak explicitly about osteogenesis imperfecta type I.

It is striking that contrary to similar operations for otosclerosis, broken and atrophic stapes crura are often found. In addition, troublesome bleeding of the footplate or of the mucosa is also seen more often. Many of the fixed stapes footplates were found to be thickened and brittle. Such findings which deviate from otosclerosis can have a

negative influence on the surgical results.

The results of stapes surgery for osteogenesis imperfecta (type I) at the Nijmegen Ear, Nose and Throat Clinic (Chapter 4) and in a large Dutch series (Chapter 5) can be classified as good. In comparison with two other large foreign series, they more than adequately bear the test of criticism.

In the long-term, it appears that there is a hearing loss of 0.8 dB per year. The average air-bone gap (air-bone conduction component) in the post-operative period hardly changed for the frequencies 0.5, 1 and 2 kHz: 9.6 dB to 11.7 dB, or 0.2 dB per year. Therefore, a large proportion (0.6 dB) of the average annual decrease in the post-operative hearing gain is the result of progression of the perceptive hearing loss. The cause most probably lies in the natural course of the disease. In Chapter 3, it was found that in a large group of 142 sufferers who had not been operated on, the average annual progression of the hearing loss was 1 dB for the frequencies 0.5, 1 and 2 kHz between the age of 10 and 45 years (0.6 dB perceptive loss and 0.4 dB conductive loss). Despite the fact that operated patients with considerable mixed hearing loss underwent stapes surgery at a relatively young age, the course of the post-operative hearing loss ran almost parallel with the natural course.

In 12 out of the 58 stapes operations in the Netherlands, we consider the initial short-term and long-term results to be disappointing (Chapter 6). In one group of six operations, no hearing gain was achieved or the hearing deteriorated in the post-operative phase, which seems to be clearly linked with the intervention. In the second group of six operations, hearing loss developed in the long-term, after what had appeared to be a good post-operative result. The incidence of complications was higher in the former group, which indicates a surgical cause for the poor results; there were also more abnormalities susceptible to complications in the middle ear. It was striking that in both groups, but particularly in the group with disappointing long-term results, the progressive, perceptive hearing loss, which is an expression of the disease itself, was manifested bilaterally. What at first appeared to be a good post-operative result can, in the course of time, change into severe hearing loss, particularly if the follow-up period is long enough, which can be observed in the symmetrical progressive occurrence of inner ear hearing loss in sufferers who were only operated on unilaterally.

We have found that the members of both groups, i.e. those with surgical complications and those with late onset progressive perceptive hearing loss, could have been recognised to some extent pre-operatively. There are several common characteristics. Firstly, they all suffered from considerable hearing loss at a young age and underwent stapes surgery at a young age. Secondly, they had a solid, thickened footplate with upturned edges which was very susceptible to bleeding. The stapes crura were thin and atrophic and the middle ear mucosa was thicker than normal and also susceptible to bleeding. Tests also showed that the pre-operative bone conduction threshold was higher than average.

In conclusion, stapes surgery for osteogenesis imperfecta is associated with more pitfalls than otosclerosis, which is clinically similar. Changes occur in the middle ear as a result of the disease itself, which give rise to a higher risk of complications and increase the risk of a disappointing result. In addition, the disease can generate a symmetrical, progressive perceptive hearing loss, which can completely destroy a good post-operative result within a few years. Nevertheless it is unjust to consider these operations a failure. The increase in inner ear hearing loss in the long-term following surgery is not the result of the intervention, but the result of the progression of the disease with increasing damage to the inner ear. Whether or not stapes surgery forms a worthwhile alternative to rehabilitation with a hearing aid should be carefully weighed up in each individual case. In view of the high risk of complications during stapes surgery for persons suffering from osteogenesis imperfecta, it is recommended to leave this operation to the most experienced otologist.

SAMENVATTING EN CONCLUSIES

INLEIDING

Eén van de oorspronkelijke doelstellingen van dit onderzoek was inzicht te krijgen in de progressie en de aard van het gehoorverlies bij osteogenesis imperfecta. In de loop van het onderzoek moest dit deel van deze studie beperkt worden tot osteogenesis imperfecta type I. Van dit type konden voldoende gegevens uit volledig onderzochte families worden verkregen om de negatieve invloed van een selectie in de onderzoeksgegevens te kunnen achterhalen en omschrijven.
Toch zijn tijdens dit onderzoek ook voor andere niet-lethale vormen van osteogenesis imperfecta voldoende ongepubliceerde audiologische gegevens verworven om te kunnen melden dat gehoorverlies niet alleen bij type I, maar ook bij type III en type IV voorkomt. Mogelijk komt het gehoorverlies bij het type III vaker en zelfs in een ernstigere mate voor, dan wij nu weten van type I. Het voortzetten van dit onderzoek voor deze andere typen van osteogenesis imperfecta wordt daarom hier bepleit.

KLINISCH GENETISCH ONDERZOEK

De segregatie van het ziektebeeld en de penetrantie van de kenmerken werden van 30 volledig onderzochte familiestambomen met 144 aselecte nakomelingen geanalyseerd. De berekende segregatie-analyse, ofwel de ratio tussen het werkelijk gevonden aantal patiënten en het op basis van een autosomaal-dominante overerving berekende aantal patiënten, bedroeg 70:72 ofwel 97%, de ideale score van 100% voor een autosomaal-dominant ziektebeeld benaderend.
De frequentiepercentages van de afzonderlijke kenmerken, zoals blauwe sclerae en botbreuken, wijken niet af van wat in de literatuur verondersteld werd, namelijk 100% voor blauwe sclerae en 87% voor fracturen. Voor het gehoorverlies wordt een gemiddeld frequentiepercentage gevonden van 43%, welke voor de opeenvolgende decaden afzonderlijk meer verschilt en leeftijdsgebonden blijkt te zijn. Het is opvallend dat het gemiddelde percentage lijders met een gehoorverlies bij diverse familiestudies overeenkomt met de alhier beschreven groep van 144 nakomelingen. De cijfers uit deze familiestudies achten wij daarom ook de juiste en wij nemen

derhalve aan dat de andere niet-familie studies, evenals onze studie vermeld in Hoofdstuk 3, gehinderd worden door een negatieve selectie. Het lijkt daarom verantwoord er voortaan vanuit te gaan dat de incidentie van het gehoorverlies bij osteogenesis imperfecta type I 43% bedraagt. Verder blijkt, na berekening van de penetrantie bij opeenvolgende generaties, dat er voor gehoorverlies een zeer duidelijke relatie bestaat tussen de leeftijd en de progressie van het gehoorverlies, wat geïllustreerd wordt in een plotdiagram (Hoofdstuk 2: figuur 2). Op oudere leeftijd blijken er nog maar weinig patienten te zijn met een normaal gehoor. De splitsing van de nakomelingen in twee groepen met of zonder een man-op-man-overerving heeft geen aanwijzingen verschaft, dat er een genetisch te onderscheiden type bestaat met een X-dominante overerving zoals bij het syndroom van Alport.

GEHOORVERLIES EN LEEFTIJD

De audiometrische gegevens van 142 lijders werden nader geanalyseerd, en omwille van het onderkennen van enigerlei selectie, vergeleken met een daaruit verkregen aselecte populatie. Het extreem hoge percentage gehoorverlies van 78% bij de 142 lijders is een gevolg van een aanzienlijke selectie op een leeftijd jonger dan 30 jaar. Na analyse van het verschil tussen beide groepen blijkt dat het om patiënten gaat uit de leeftijdscategorie 10-30 jaren, met een gemiddeld niveau van gehoorverlies van 30-50 dB, de grens van het sociaal horen overschrijdend.

Wanneer onze onderzoeksgegevens gecorrigeerd worden voor de eerder beschreven negatieve selectie, kan als volgt geconcludeerd worden. Het gemiddelde gehoorverlies neemt tussen het 10^e en 45^e jaar met 1 dB per jaar toe voor de frequenties 0,5-2kHz, met 1,1 dB per jaar voor 4kHz, en met 1,7 dB per jaar voor 8kHz. Daarvan bedraagt de conductieve component voor alle frequenties constant 0,4 dB gedurende de gehele periode. Voor patiënten in de postoperatieve fase na stapeschirurgie bleek eerder reeds (Hoofdstuk 5) dat een afname van het gehoor van ongeveer 0,8 dB per jaar te verwachten is. Dit verlies blijkt vrijwel volledig van perceptieve aard, mede gezien het vrijwel constant blijven van het verschil tussen de been- en luchtgeleidingsdrempels in de follow-up periode.

De thans voorhanden zijnde gegevens tonen de progressie van het gehoorverlies, zowel van conductieve als van perceptieve aard, met de leeftijd. Voor het eerst is het gelukt deze progressie tussen het 10e en 45e jaar nader te omschrijven. De gegevens tonen tegelijk een duidelijke spreiding in ernst van het gehoorverlies, ook voor dezelfde leeftijdsklasse. Het geleidingsverlies wordt ook niet obligaat zo groot dat doorgaans een indicatie voor stapeschirurgie zal ontstaan. Toch is de kans dat een lijder aan osteogenesis imperfecta type I tijdens de volwassenheid met een fors gehoorverlies als gevolg van de ziekte geconfronteerd zal worden naar ons oordeel tamelijk groot. Wij menen daarom dat het optreden van gehoorverlies, naast andere belemmerende factoren die kunnen voortvloeien uit het ziektebeeld, waaronder fracturen, ook een factor is die de beroepskeuze zou mogen beïnvloeden. Vooral in de communicatief ingestelde beroepen waar men temidden van achtergrondsgeluiden de spraak steeds moet kunnen verstaan, zal deze auditieve handicap het eerst hinderlijk worden. Wanneer het om aanzienlijke binnenoorverliezen gaat zal voor moeilijke luisteromstandigheden revalidatie met een hoortoestel onvoldoende uitkomst bieden. Het duurzaam ontwijken van deze moeilijkere luisteromstandigheden, met name een geluidsrijke omgeving, zal op oudere leeftijd niet voor een ieder in elke professie mogelijk zijn. Mogelijkheden voor omscholing hebben ook hun beperking. Wij menen daarom dat het juist zou zijn om de huidige toch nog beperkte kennis over de kansen op een progressief gehoorverlies bij lijders aan osteogenesis imperfecta type I mede overwogen wordt bij het maken van een beroepskeuze of een keuze voor een beroepsopleiding.

STAPESCHIRURGIE

Alhoewel in de hoofdstukken 4, 5 en 6 over stapeschirurgie evenals in de 2 andere grote series in de literatuur niet expliciet vermeld wordt dat het bij deze lijders steeds om osteogenesis imperfecta type I gaat, geldt dit wel voor de meesten mogelijk zelfs voor hen allen. Bij een geïsoleerd voorkomen van osteogenesis imperfecta met ook al op jeugdige leeftijd een gehoorverlies en ernstige verschijnselen ten gevolge van vele factoren kan men zeker bij een retrospectieve studie op dit punt enige aarzeling

ervaren. Het is daarom dat de auteurs er de voorkeur aan hebben gegeven hier niet expliciet te spreken over osteogenesis imperfecta type I.

Opvallend is dat in tegenstelling tot bevindingen bij vergelijkbare operaties voor otosclerose, er vaak gebroken en atrofische stapes crura worden gevonden. Ook een hinderlijke bloeding van de voetplaat of van de mucosa wordt meer gezien. Veel gefixeerde stapesvoetplaten blijken verdikt en broos te zijn. Deze van otosclerose afwijkende bevindingen kunnen het operatieresultaat in ongunstige zin beïnvloeden.

De resultaten van stapeschirurgie bij osteogenesis imperfecta (type I) voor zowel de Nijmeegse Kliniek voor KNO-heelkunde (Hoofstuk 4) als die voor een grote Nederlandse serie (Hoofdstuk 5) zijn zonder meer als goed te beschouwen. In vergelijking met twee andere grote buitenlandse series, kunnen zij de toets der kritiek ruim doorstaan.

Op lange termijn blijkt dat er een afname van de gehoorwinst van 0,8 dB per jaar optreedt. De gemiddelde air-bone gap (lucht-beengeleidingscomponent) in de postoperatieve periode voor de frequentie's 0.5, 1, en 2kHz verandert nauwelijks, namelijk van 9.6 dB naar 11.7 dB, ofwel 0,2 dB per jaar. Daarom zal een groot deel (0,6 dB) van de gemiddelde jaarlijkse afname van de postoperatieve gehoorwinst een gevolg moeten zijn van een progressie van het perceptieve gehoorverlies. De oorzaak hiervan lijkt het gevolg van het natuurlijke verloop van de ziekte. Reeds eerder was bij een grote groep van 142 niet-geopereerde lijders komen vast te staan, dat er een jaarlijkse progressie van het gehoorverlies optreedt van gemiddeld 1 dB over de frequentie's 0.5, 1, en 2kHz tussen het 10^e en 45^e jaar, waarvan 0,6 dB van perceptieve en 0,4 dB van conductieve aard (Hoofdstuk 3). Ondanks het feit dat geopereerde patienten op relatief jonge leeftijd en met een aanzienlijk gemengd gehoorverlies stapeschirurgie ondergaan, blijkt dat bij hen het gehoorverlies postoperatief vrijwel gelijk op gaat met het natuurlijke verloop.

Bij 12 van 58 stapes operaties in Nederland worden de resultaten door ons aanvankelijk op de korte of de lange termijn als teleurstellend beschouwd (Hoofdstuk 6). Eén groep van 6 operaties kent een uitblijven van gehoorwinst of een gehoorverlies in de postoperatieve fase, zodat een relatie met de ingreep vanzelfsprekend lijkt. Daarentegen ontwikkelt bij een tweede groep van 6 operaties het gehoorverlies zich op lange termijn, na een in eerste instantie goed postoperatief

resultaat. In de eerste groep doen zich vaker complicaties voor, zodat een chirurgische oorzaak voor het slechte resultaat aanwijsbaar lijkt. In die groep blijken tevens meer complicatie gevoelige afwijkingen in het middenoor aanwezig te zijn. Opvallend voor beide groepen, maar met name voor de groep met het teleurstellende resultaat op lange termijn, is het feit dat een progressief perceptief gehoorverlies, een uiting van de ziekte zelf, zich bilateraal manifesteert. Een ogenschijnlijk goed postoperatief resultaat kan in de loop der jaren veranderen in een ernstige slechthorendheid, zeker indien de follow-up periode lang genoeg is, wat waar te nemen valt aan het symmetrisch progressief optreden van een binnenoorverlies ook bij slechts aan één oor geopereerde lijders.

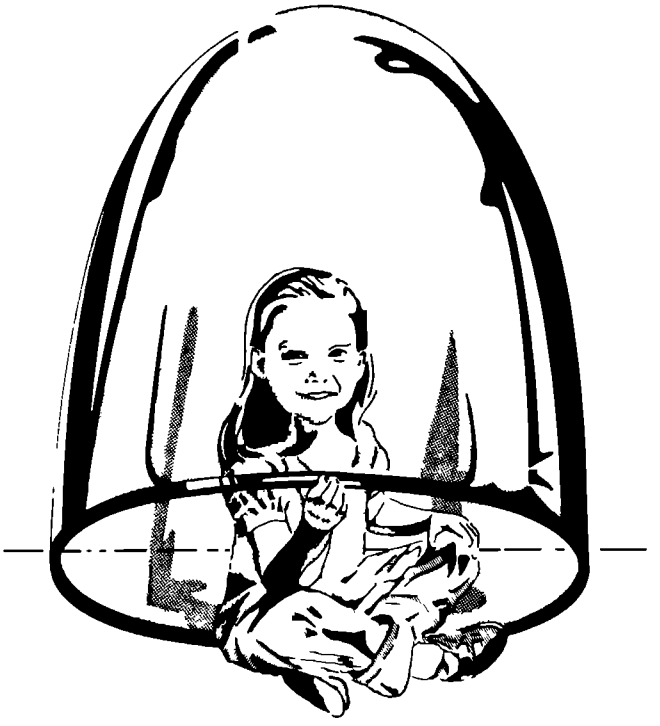
Voor beide groepen, zowel die met complicaties tijdens de operatie als die met het later intredende progressieve perceptieve gehoorverlies, blijkt dat zij ten dele preoperatief herkend kunnen worden. Er zijn enkele gemeenschappelijke eigenschappen. Allereerst blijkt dat zij reeds op jonge leeftijd een aanzienlijk gehoorverlies hebben, en al op jongere leeftijd stapes chirurgie hebben ondergaan. Daarnaast hebben zij een massief verdikte voetplaat met opgeworpen randen en een makkelijk optredende bloeding. De stapespootjes zijn dun en atrofisch, en de middenoormucosa is dikker dan normaal, wat een hinderlijke bloeding tot gevolg kan hebben. Ook blijkt dat de preoperatieve beengeleidingsdrempel veel ongunstiger is dan gemiddeld.

Concluderend blijkt dat stapeschirurgie bij osteogenesis imperfecta meer valkuilen met zich meebrengt dan bij het klinisch vergelijkbare ziektebeeld otosclerose. Door de ziekte zelf ontstaan er veranderingen in het middenoor welke een verhoogde kans op complicaties geven en die de kans op een teleurstellend resultaat kunnen doen toenemen. Daarnaast kan de ziekte een symmetrisch optredend progressief perceptief gehoorverlies genereren, welke een postoperatief goed resultaat binnen een aantal jaren volledig kan laten verdwijnen. Het is echter onterecht om deze operaties als een mislukking te beschouwen. De na de operatie op langere termijn ingetreden toename van het binnenoorverlies is niet een gevolg van de operatie, maar van de progressie van de ziekte met een toenemende schade aan het binnenoor. De beoordeling of stapeschirurgie een verantwoord alternatief biedt ten opzichte van prothetisering met behulp van een hoorapparaat behoeft steeds een afweging in het individuele geval.

Gezien een verhoogde kans op complicaties bij stapeschirurgie bij lijders aan dit ziektebeeld wordt aanbevolen deze chirurgie over te laten aan de meest ervaren otologen.

APPENDICES I

SAXE PORCELAIN



"When I was a child, my mother, who often invented pet names, used to call me 'my little saxe porcelain doll'. As young as I was, I did not connect any special meaning to it; I just thought it was nice. It was not until much later that I realized that it was a very apt description. I have no knowledge of ceramics; as far as 'saxe porcelain' is concerned, I can make vague associations with soul-stirring, pastoral, sculptured shepherdesses in sweet-voiced colours. But also with 'rare', 'vulnerable' and 'fragile'. And while I am writing this, with 'priceless', a meaning that my mother undoubtedly also intended.

Anything that is vulnerable and delicate is generally treated with care and prudence. And that is now the very crux of the matter, what it is all about for we unfortunate souls suffering from such a treacherous condition, with an oh so pretty-sounding name. Osteogenesis imperfecta; it sounds like a flower or a type of bird, to those who have not studied Latin. But the truth is different. A life which from the very first awakening of the child (and her family!) is marked by pain, worry and isolation on the one hand and the urge to join in like everyone else does in society on the other. Because why shouldn't we, with our life-long wariness of danger, want go to school like other people, want to play with children of our own age, train for a job, find a partner and bring up children ourselves?

To gain experience, which is such a natural thing for everybody else, we have to wage a fight. A fight with a variable outcome on the 'battle field'. Often our victories are followed by regressions which are difficult to swallow. Afterwards - and this has struck me since I have met other people with OI - after a long or short period of time, we return once again to the battle field. For whatever might have gone wrong with our genes, there is nothing wrong with our will power. This is of the utmost importance to people with this particular illness.

If you are a spastic, or have rheumatism or polio, your life will undoubtedly be full of obstacles too. But there is one great difference: most people have at least heard of

the condition and have some sort of idea what it is - correct or not. Conversely, if you say, 'I have got osteogenesis imperfecta', hardly anyone knows what that is. (Haven't I been confronted so often with people in the medical profession who admit that they have to look it up in their books first, because the name rings a bell, 'but it is such an uncommon condition'). This sort of thing makes many of us shy away, and sometimes just weary. How are you supposed to explain time and time again that a cold hand grips your heart if someone shouts joyfully, 'Hey, it is going to snow!'; or that you worry if you have to go somewhere where they have just laid a beautiful new marble floor; or that when a dog runs up to you in the street it nearly scares you stiff, even though a passer-by says in a well-meaning way, 'Oh, he won't hurt you' ... No, he won't hurt me, but you stand there every time frightened silly. One wrong move, a fall, and you will be out of circulation again for weeks. More pain. Once again dependent on others.

Prudence and care, they don't leave you alone for a second. And you can't explain that to all the 'passers by' in your life. Who does understand? Your family who have looked after you since the first day and - if you are lucky enough to have one - your partner or a good friend. Because explaining costs such a lot of energy and often, unintentionally, meets with a lack of understanding, we don't bother and end up forcing ourselves yet again. Still we enter the bank with the slippery floor, still we go outside in an autumn storm, still we wait patiently in the queue at the check-out, still we join in with everybody else.

In this way we search every day for the brittle balance between the isolation of our limitations and the satisfaction of victory. And the latter - the relative victory over what we can do - is determined for the large part by will power. Will power is the priceless item that we grasp so tightly. Everybody searches for balance in his or her own way and that takes will power. My mother was right with her 'saxe porcelain'. It might be delicate and rare, but it is also priceless."

Annemiek de Groot

"Toen ik nog een kind was noemde mijn moeder, die zich vaker van koosnaampjes bediende, mij 'poppetje van saksisch porselein'. Klein als ik was, verbond ik geen speciale betekenis aan deze benaming; ik vond het enkel leuk. Pas veel later begreep ik dat dat een zeer juist gevonden betiteling was. Ik ben geen kenner van keramiek; bij 'saksisch porselein' heb ik vage associaties met pathetische beeldjes van pastorale herderinnetjes in zoetgevooisde kleuren. Maar ook met 'zeldzaam', 'kwetsbaar' en 'fragiel'. En terwijl ik dit schrijf, met 'kostbaar', een betekenis die mijn moeder er ongetwijfeld óók mee bedoeld heeft.

Dat wat kwetsbaar en teer is wordt doorgaans met zorg en voorzichtigheid behandeld. En dát is nu juist de crux, waar het bij ons, lijders aan de zo verraderlijke ziekte met de o zo fraai klinkende naam, om draait. Osteogenesis imperfecta; het lijkt wel een bloem of een vogelsoort, voor hen die het latijn niet zo machtig zijn. Maar de realiteit is anders. Een leven dat vanaf de allereerste bewustwording van het kind (en van de familie!) wordt gekenmerkt door enerzijds angst, pijn en isolement, anderzijds de drang om gewoon mee te willen doen in de maatschappij. Want waarom zouden wij, met onze levenslange waakzaamheid voor gevaar, niet nèt als ieder ander naar school willen gaan, met leeftijdsgenootjes willen spelen, een baan willen krijgen, een partner willen vinden en zelf kinderen willen opvoeden?

Om al die ervaringen, die voor willekeurig welk ander mens zo vanzelfsprekend zijn, te kunnen opdoen, moeten we strijd leveren. Een strijd met een wisselend verloop op het 'slagveld'. Vaak wordt een overwinning weer gevolgd door een maar weer moeilijk te verkroppen terugval. Waarna, en dat is me opgevallen sinds ik meer mensen heb leren kennen die ook OI hebben, na kortere of langere tijd het slagveld weer opnieuw betreden wordt. Want wát er ook fout mocht zijn gegaan met onze genen, aan onze wíl mankeert niets! Juist bij deze ziekte is dat zo belangrijk.

Als je spastisch bent of reuma hebt of polio, heb je ongetwijfeld nèt zo'n leven vol obstakels. Maar er is één verschil: de meeste mensen hebben er wel eens van gehoord

en hebben er een -al dan niet juiste- voorstelling van. Als je daarentegen zegt: "ik heb osteogenesis imperfecta" weet praktisch niemand wat dat is. (Zelf heb ik toch ook regelmatig meegemaakt dat hulpverleners uit de medische hoek te kennen gaven eerst even in hun boeken te moeten kijken, omdat ze wel de klok hadden horen luiden, maar ja "het komt ook zó weinig voor"). Dát maakt velen van ons kopschuw en soms gewoon móe. Hoe kun je keer op keer uitleggen dat er een koude hand om je hart grijpt als iemand verheugd uitroept "Ha, het gaat sneeuwen!"; dat je bang bent als je ergens zijn moet waar nèt een prachtige nieuwe marmeren vloer is gelegd; dat een rennende hond op straat je de stuipen op het lijf jaagt, al zegt een voorbijganger goedbedoelend "Ach, hij doet niks" ... Nee, hij doet niets, maar jij staat elke keer weer doodsangsten uit. Eén verkeerde beweging, een val, en je bent weer voor weken uit de roulatie. Weer pijn. Weer afhankelijkheid van anderen.

Voorzichtigheid en zorg, het laat je geen seconde los. En dát is niet uit te leggen aan al die 'voorbijgangers' in je leven. Wie het wel begrijpen: je familie, die de zorg vanaf de eerste dag heeft gedeeld en -als je geluk hebt die te hebben- je partner of een goede vriend. Omdat het uitleggen zoveel energie kost en vaak op onbedoeld onbegrip stuit, láten we het maar en forceren we ons al te vaak maar weer. Tóch maar weer die bank in met die gladde vloer, toch maar weer naar buiten als er een herfststorm woedt, tóch maar weer geduldig wachten in de rij voor de kassa, tóch maar weer méédoen met de anderen.

Zo zoeken we elke dag weer een broos evenwicht tussen het isolement van onze beperkingen en de voldoening van de overwinningen. En dat laatste -de relatieve overwinning op onze mogelijkheden- wordt voor een groot deel bepaald door wíl. Dat is het 'kostbare' wat we in handen hebben. Ieder zoekt dat evenwicht op zijn eigen wijze en daarvoor is wíl nodig. Mijn moeder had gelijk met 'saksisch porselein'. Het mag dan teer zijn en zeldzaam, het is ook kostbaar!"

Annemiek de Groot

APPENDICES II

CONTRIBUTING SURGEONS

The following Dutch ear-nose and throat surgeons provided material from the patients with osteogenesis imperfecta who underwent ear surgery:

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P.H. Dijkstra, Breda
R.B. Engelsma, Rotterdam
Prof. Dr. L. Feenstra, Amsterdam (nowadays; Leuven)
Dr. G.A. Hoogland, Arnhem (nowadays; Berg en Dal)
Prof. Dr. E.H. Huizing, Utrecht
Dr. H. Jongert, Rotterdam
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The author was born on December 27th, 1953 in Arnhem. After finishing secondary school, he completed military service for two years.
He studied medicine at the Medical Faculty of the Catholic University of Nijmegen from 1975 to 1983.
He worked as a resident in Neurosurgery at the Neurosurgical Center of Nijmegen under the supervision of Prof. Dr. E. Meijer (1984 - 1985).
He started in 1985 as research-fellow at the Department of Otorhinolaryngology (Head: Prof. Dr. P. van den Broek), University Hospital Nijmegen.
From 1986 to 1991 he received training in Otorhinolaryngology at the Department of Otorhinolaryngology (Head: Prof. Dr. P. van den Broek), University Hospital Nijmegen. He was registered as ENT-surgeon on January 1st, 1991.
At present the author is working at the Medical Center Alkmaar.
The author married on May 11th, 1983 to Anne-Marie van Loon. They have three children Daan, Anne and Sjoerd.

STELLINGEN

behorende bij het proefschrift

OSTEOGENESIS IMPERFECTA TYPE I

OTOLOGICAL AND CLINICAL GENETIC ASPECTS

A.J.T.M. Garretsen

Nijmegen, 11 mei 1992

1. Het voor osteogenesis imperfecta kenmerkende gehoorverlies komt bij alle vormen van osteogenesis imperfecta voor.

2. Binnen een niet-geselecteerde populatie van lijders aan osteogenesis imperfecta type I bedraagt de prevalentie van gehoorverlies 43%.

3. Bij lijders aan osteogenesis imperfecta type I is tussen het 10^{e} en 45^{e} levensjaar een progressief gemengd gehoorverlies te verwachten, dat gemiddeld 1 decibel per jaar toeneemt.

4. Het is gerechtvaardigd bij mensen met een gemengd gehoorverlies veroorzaakt door osteogenesis imperfecta, op jonge leeftijd een stijgbeugel-vervangende operatie te verrichten, mede gezien de te verwachten progressie van het perceptieve gehoorverlies.

5. De teleurstellende resultaten na een stijgbeugel-vervangende operatie bij osteogenesis imperfecta mogen niet zonder meer de operateur worden aangerekend.

6. Een stijgbeugel-vervangende operatie bij osteogenesis imperfecta behoort plaats te vinden in de handen van ervaren otologen, die met de ziekte bekend zijn.

7. Men dient ervoor te waken, dat ouders van kinderen met recidiverende botbreuken niet verdacht worden van kindermishandeling, of zelfs uit de ouderlijke macht worden ontzet, alvorens osteogenesis imperfecta als mogelijke oorzaak is uitgesloten.

8. Voor het aantonen van het syndroom van Sjögren is het voldoende de reumafactoren en het anti-SS-B en anti-SS-A in het serum te bepalen.

9. Door de grote kans op een vals-negatieve uitslag van het sialogram bij het syndroom van Sjögren is de waarde van dit onderzoek als diagnosticum achterhaald.

10. Er zijn geen erger doven dan die niet horen willen.

11. De vindingrijkheid van de partner van de promovendus neemt evenredig toe met de duur van het promotie-onderzoek.